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THAT I worked under and with Pirquet was a life experience which cannot be overestimated, because it means that for many years I was in close contact with a genius. His personality, character, and active brain influenced my whole life, and had their effect on everybody around him. Pirquet's love for the truth, his respect for and understanding of his fellowmen, his liberalism, his joy in helping others, his complete lack of envy or jealousy, made everyone around him better human beings and prevented anyone from approaching him with unworthy motives. Only once did I see him angry, and this was during the Austrian revolution after the First World War, when officials of the government mistreated members of the medical faculty, whereas the revolutionary forces were treated with the softest kind of gloves. Employes of the hospital, including the wash and scrub women, were all considered more important than the physicians.

Pirquet never wanted to listen to derogatory remarks made by one staff member about another. Such comments were taboo. All members of the medical staff worked quietly on their respective problems. There were no factions within the staff. We were all busy concentrating our efforts on building up a children's department that would be respected by the pediatric world, and by ourselves. Life in the clinic was peaceful.

I met Pirquet for the first time when we were medical students in Graz.

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Presented by Dr. Schick on the occasion of a dinner given Wednesday, May 23, 1956, by the Board of Trustees of the Mt. Sinai Hospital and the New York Allergy Society, at the semi-centennial exercises commemorating Clemens von Pirquet and Dr. Béla Schick.

The number of students in our class was very small, approximately thirty, so that we all knew each other, at least by sight. The Department of Internal Medicine had no auditorium, so we sat on ordinary chairs around our beloved teacher, Friedrich Kraus, literally at his feet. I realized what an advantage we students had to be so close to our great teachers. Pirquet was always with his friend Haberer, who later became an outstanding surgeon. Both were excellent students and were always the first to be ready to take the examination and, therefore, were the first of our group to graduate.

At the time of graduation it is frequently difficult to plan one's future. At first, I had to complete my military service; afterwards I entered the clinic of internal medicine, where I stayed almost a year, and then joined the psychiatric department of Prof. Anton for four months. Finally, in the fall of 1901, having decided to become a pediatrician, I started to study pediatrics under Escherich. Very soon thereafter he was called to Vienna to become the successor of Prof. Widerhofer. For several months I remained in the children's clinic in Graz, studying under Prof. Pfaundler; then, like the other members of the staff, I followed Escherich to Vienna. There I became a volunteer (Aspirant) in the pediatric clinic. Moser, who was the first assistant, asked me whether I was afraid to work in the scarlet fever ward; after replying that I was not afraid, I was assigned to the scarlet fever pavilion. To my great surprise, I learned that Pirquet was the physician in charge of the scarlet fever pavilion. It is interesting how kind fate can be, at times, to an individual. For me, it was like a fairy tale. Moser had just discovered an effective and specific anti-streptococcus serum against scarlet fever. Pirquet had had the opportunity to study the effect of this serum and now I joined him. Large amounts of serum were needed. One to two hundred cubic centimeters were injected, but such a dosage produced serum sickness in almost one hundred per cent of the patients. It was here that Pirquet made his observations which led to the discovery of Allergy.

Patient Egon H. was injected with Moser serum in September, 1902, developing serum sickness (fever, rash) after an incubation time of seven days. On November 2, 1902, several cases of diphtheria were discovered in the ward, and it was decided to prevent the outbreak of new cases of diphtheria by prophylactic injections of 2 cc of diphtheria antitoxin. To Pirquet's great surprise, ten minutes after Egon H. was injected he became sick, vomited very soon afterwards, edema of the lips and face appeared, and a typical urticarial eruption followed. Such sudden reactions following the injection of serum had been seen before by other observers, but they did not realize that these reactions occurred only in children who had been previously injected, and never occurred after a first injection of serum. They reported the rapid appearance of serum sickness and let it go at that; but not Pirquet, and this is characteristic of a genius. He pondered what could have caused this change in the

duration of the incubation time, and what might be the full importance of such an unusual phenomenon.

At first the incubation time had to be explained. In primary toxic so-called exotoxic diseases like diphtheria, it is the time needed for the diphtheria bacillus to produce enough toxin to develop the disease. It is evident that the length of the incubation time depends upon the amount and potency of the toxin. In endotoxic diseases like smallpox vaccination, typhoid fever and tuberculosis, it is the time needed for the mobilization of bacteriolytic or virolytic and bacteriocidal or virocidal antibodies in order that they may stop the multiplication of the pathogenic *agens* and destroy it. In this way the endotoxin enclosed in the *agens* is set free. Endotoxin is, as such, toxic; no anti-endotoxin exists. Eight to twelve or fourteen days elapse until the liberated endotoxin starts the disease, and the disease is the price which our organism must pay for the termination of the infection.

Serum sickness is due to the parenteral injection of foreign protein. Here we find an incubation time similar to that found in an endotoxic disease. Serum is a dead substance, as such not toxic, contains no bacteria nor endotoxin, and does not multiply. The previously given explanation of the incubation time is not applicable to serum disease, as an explanation of the incubation time of this disease must contain the answer to the question why the incubation time in reinjected individuals is either missing or shortened.

After Pirquet and I studied all the details of serum sickness for three years, we published our monograph in 1905 in which we reported the following theory. Horse serum, as a foreign protein, is not tolerated when injected parenterally and must be destroyed. We can assume that this destruction is similar to the digestion of protein in our intestinal tract where foreign protein is daily destroyed by digestive juices. The protein is rapidly broken down to amino acids. Protein and amino acids are not toxic. During the digestion of the protein, intermediary toxic substances appear which are detoxified within the intestinal wall, and, after absorption, are further detoxified by the liver. If protein is injected parenterally, the destruction has to be carried out by the cells of the organs. These cells are not as well prepared as the cells of the intestinal tract; they are only potentially able to mobilize antibody-like substances for the digestion of the protein. The mobilization of these antibodies needs time —this is what we call the incubation time. The breaking down of the protein is carried out in a way that is similar to the digestion of the protein in our intestinal tract. Here, also, toxic intermediary substances are created during the interaction of protein as antigen with its antibodies. These toxic substances are not readily detoxified; therefore, symptoms of serum sickness ensue. Antibodies, once created, stay in circulation for about four months, then slowly disappear. If serum is reinjected within four months, it immediately interacts with the still present antibodies, and

no incubation time is needed. Symptoms of serum sickness can appear almost instantly after the injection. After the elapse of more than four months since the first injection antibodies are no longer present; however, the cells of the organism acquired some skill due to the first injection, and the mobilization of antibodies therefore needs less time. When, therefore, reinjection takes place more than four months after the first injection, interaction between antigen and antibody can occur earlier than after the first injection. After four to six days, symptoms of serum sickness already appear, and this is called an accelerated reaction. Let me repeat that this altered reactivity has diagnostic value. Immediate and accelerated reactions have another characteristic feature. They are more intensive and can even be so violent that the patient may go into shock and may even die.

Here I wish again to point out Pirquet's remarkable ability to grasp the full import of all his observations. Many other investigators would have been satisfied to report a very interesting phenomenon. Pirquet's brain worked differently. He was convinced that the change of reactivity has a much more important meaning. As antibodies have been interacting with a pathogenic *agens,* he wondered what would happen in infectious diseases where the mobilization of antibodies also takes place. Will an altered reactivity exist at the time of reinfection and, if so, will this altered reactivity lead to immunity? For the study of this problem Pirquet selected a disease which is particularly suitable for experimental investigation—smallpox vaccination. Furthermore, the most striking features of the disease were easily visible on the skin, and the appearance, development, and course of the reaction could be measured. In order to have a uniform field of infection, Pirquet constructed an instrument called a borer. It was in this way that Pirquet established the fact that altered reactivity—immediate and accelerated reactions as seen in serum sickness—also existed in smallpox vaccination. The established immunity could be readily observed. In serum sickness the altered reactivity was, as we have already mentioned, useless, annoying, and even dangerous; moreover, it did not lead to immunity. Pirquet recognized that the situation in infectious diseases was quite different. The mobilization of antibodies against an infectious disease initiates the disease and also leads, through the killing of the invading germ, to the end of the disease. The persistence of the antibodies in the organism guarantees, in case of reinfection, an immediate destruction of the invading germ. An insignificant amount of toxic substance (endotoxin) is set free, most frequently not producing visible symptoms. Even an accelerated reaction minimizes the intensity of the disease. The reactions are beneficial and demonstrate clinical immunity.

Mindful that the usual explanation of immunity was quite different, Pirquet decided that a new term was necessary for expressing the new concept. In a paper published fifty years ago in the *Münchener Medi-*

zinische Wochenschrift on the twenty-fourth day of July, 1906, Volume 53, he explained the new term "Allergy." A reviewer, whose name I no longer remember, found it appropriate to declare that Pirquet's paper was an unimportant and superfluous publication introducing a new and useless word. I hope that this reviewer has meanwhile learned what a great mistake he made.

As in serum sickness, immediate and accelerated reactions had diagnostic value also in infectious diseases. Fortunately, Pirquet had the satisfaction to live to see that his work was a master stroke. Every day allergy is discovered to have new applications in medicine. Rheumatic infection, lupus erythematosus, collagen disease, periarteritis nodosa, nephritis, and innumerable other diseases show allergic features. Nature cannot exist without using allergy as a defense mechanism. Allergy has created a new specialty of medical practice, the specialty of allergic diseases. All allergic symptoms of these diseases follow the paradigma of serum sickness and are due to protein-containing substances. The mechanism of defense does not bring about immunity. Only two methods of treatment are available; the one consists of finding out the offending substance and then avoiding it, the other method tries to desensitize the patient by repeated injections of the offending substance in slowly increasing doses. In order to find out the substance responsible for the clinical symptoms, skin testing is used.

After completing his study of smallpox vaccination, Pirquet focused his attention upon tuberculosis. In the year 1895, Koch had developed his famous tuberculin test which consisted of fever following the subcutaneous injection of 0.01 cc old tuberculin. A positive fever reaction indicated the presence of active tuberculosis. Koch thought that nontuberculous individuals reacted with fever only to a larger amount of tuberculin. He did not realize that tuberculin was not at all toxic for individuals entirely free of tuberculosis. Many experimental findings pointed to the advisability of investigating the positive tuberculin reaction with the idea of allergy in mind. Pirquet was, at first, not very enthusiastic about the supposition that tuberculin be included among the allergens. He wanted to have more facts. I tried very hard to convince him that a tuberculin reaction was allergic in nature. Many years prior to this, Escherich had studied the Koch tuberculin test in pediatrics and accepted its diagnostic value, and Pirquet sent me to Graz to review the cases observed by Escherich. It was very interesting that Escherich, and after him Epstein, had observed in some cases a local, inflammatory reaction to tuberculin at the site where the tuberculin had been injected. The reaction was called Stich-Reaction. I found that the Stich-Reaction was specific like the fever reaction. With these developments, Pirquet became more inclined to accept tuberculin as a diagnostic allergen. He then had the brilliant idea to use the borer, which he had applied so successfully in his study

of smallpox vaccination, for a skin test for tuberculosis. Thus the cutaneous (scratch) test for tuberculosis was born.

A tremendous number of papers were written which corroborated Pirquet's statement that the tuberculin scratch test was a reliable test for discovering the existence of a tuberculous focus in an infant or child. Furthermore, the tuberculin test, supported by x-ray examination of the child and its family, became an extremely valuable weapon in the fight against tuberculosis. Pirquet now became world famous. He was invited to the United States, where he was appointed Professor of Children's Diseases at Johns Hopkins University in Baltimore, Prof. Welsh, who recognized the outstanding work of Pirquet, being responsible for the appointment. Here Pirquet spent the happiest days of his life.

It is sad to relate that the simple cutaneous tuberculin test has been replaced by an intracutaneous test called the Mantoux test, and that the name Pirquet test is almost forgotten. Questioning medical students about the tuberculin test, I found that they only knew the Mantoux test and the Vollmer patch test.

Tuberculin is a peculiar substance, and Pirquet was right to have hesitated to accept it as an allergen. Some of its peculiarities are still not completely understood; for example, one cannot produce an allergy against tuberculin by repeated tuberculin injections. Until lately, passive transfer was impossible to demonstrate. The composition of tuberculin is very complicated, and the tuberculin reaction is not like most of the common allergic reactions—wheal-like or urticarial-like reactions—but is an inflammatory, slow developing reaction. However, these difficulties do not interfere with the reliability of the test.

In conclusion, I wish to point out again that the main features of allergy are part of a physiologic defense mechanism of nature and are beneficial to us, as they help control infectious diseases and bring about immunity. Some features, however, particularly diseases due to protein substances, are characterized by useless, painful, and even dangerous pathologic reactions.

Nature is well prepared for its fight against our enemy number one, the pathogenic bacterium or virus, but not so well prepared for the destruction of foreign protein. Nature applies the same defense mechanism in both conditions. In protein allergy, unfortunately, toxic substances are created and no immunity is established. This pathologic form of allergy is only a small part of allergy. The physiologic and beneficial forms of allergy leading to immunity embrace a much greater field. Let us teach the students of medicine the great discoveries of Pirquet, who coined the term allergy and realized its importance for the entire science of medicine. Allergy, for many years to come, will continue to play an important role in our medical thinking.

1045 Park Ave.
Submitted May 23, 1956

CONSIDERATIONS OF SPECIAL INTEREST TO THE ALLERGIST ON THE COMPOSITION AND PRODUCTION OF POLIOMYELITIS VACCINE

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THE introduction and broad scale use of the Salk poliomyelitis vaccine have probably been the subjects of more discussion among professional and lay groups than any other issues in recent medical history. Nevertheless, for one reason or another, it is apparent that a significant amount of confusion still exists, as would be expected concerning an immunizing agent so recently introduced. Much remains to be learned about the preparation and use of this vaccine. Although it is a giant step in the right direction, the present vaccine is by no means considered the final answer to the need of an effective immunizing agent against paralytic poliomyelitis. Indeed, many improvements have already been made in the techniques of preparation, testing and use; and means to improve it further are constantly being sought and studied by various research groups, including those of industry. Investigations of other completely different types of vaccines are also in progress.

We believe that allergists and immunologists would be interested in learning in some detail, about the ingredients and methods of preparation of poliomyelitis vaccine. As you know, considerable concern has been expressed relative to the possibility that certain of the ingredients, in the quantities present, may be capable of inducing primary sensitization or of producing allergic reactions in those already hypersensitive. Therefore, I should like to present 1) a brief review of the literature, including several of the investigations that have been carried out to define more clearly the "allergenic liability" of some of the ingredients, and 2) a summary of our experience gained from several clinical studies pertaining to the apparently low incidence of allergic reactions following administration of poliomyelitis vaccine.

Poliomyelitis vaccine is prepared by growing representative strains of the three known immunologic types of poliomyelitis virus in tissue cultures. Kidney epithelial cells from rhesus *(Macaca mulatta)* and cynomolgus *(Macaca irus)* monkeys have been found the most suitable tissue for growth and multiplication of this virus. To enable growth of the monkey kidney tissue and poliomyelitis viruses *in vitro*, media containing nutrients and antibiotics are necessary. Later processing includes addition of a chemical agent to inactivate the virus, a compound to neutralize the inactivating agent, and preservatives, which are essential to any biologic

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preparation dispensed in multiple dose containers, to prevent bacterial contamination.

As you know, poliomyelitis vaccine, like any other biologic product, is prepared and tested according to the minimum requirements established by the Division of Biologic Standards, National Institutes of Health, United States Public Health Service, Department of Health, Education and Welfare. Some latitude, however, is allowed in the minimum requirements. For instance, the individual manufacturer has a choice of the antibiotics to be used during processing and the preservatives to be added. It can be said that all the Salk vaccines available today from the different manufacturers are very similar but some minor differences do exist. Despite these differences, all must meet the established standards for safety, potency and purity. Naturally, I am familiar with the Wyeth vaccine only, and this presentation is, of necessity, limited to the Wyeth product.

Preparation of poliomyelitis vaccine begins with careful cleansing, rinsing and sterilization of all glassware to be used in the process. Povitsky bottles are considered suitable for the purpose of growing the monkey kidney cells. A specified amount of trypsinized fresh monkey kidney cells is added to Povitsky bottles containing synthetic medium 199[1] and 0.5 per cent horse serum. The presence of animal serum is necessary to "start" the cultures. Synthetic medium 199, which was developed by Morgan and associates at Connaught Laboratories, is a mixture of amino acids, salts, vitamins, minerals and an indicator, phenol red (phenolsulfonephthalein). The concentrations of the ingredients per liter are listed in Table I. Most of these substances are essential for *in vitro* growth of living cells. A solution of penicillin G, neomycin and dihydrostreptomycin is also added in amounts sufficient to bring the final concentrations to 200 units, 0.1 mg and 0.2 mg per cc, respectively. The ability to prevent bacterial contamination in tissue culture systems by addition of bactericidal antibiotics has probably been one of the most important factors in the advancement of tissue culture research. The technique of tissue culture has been known for many years but successful mass application was neither possible nor practicable until antibiotics provided a means of preventing bacterial contamination.

The mixture of kidney cells and antibiotic-containing medium 199 is incubated for approximately seven days. On inspection at this time a sheet of kidney cells will be seen growing on and adherent to the bottom of the bottle. The next step is infection of the cultures with a specified amount of the seed poliomyelitis virus of the desired type (1, 2 or 3). Before this is done, however, the medium (bathing the growing cells) is drawn off and the sheets of cells are washed twice with Hank's balanced salt solution, to which no antibiotics or animal serum have been added. Then, fresh medium 199 is introduced to refeed the kidney cells and a little later the poliomyelitis virus is added. This series of washings and

TABLE I. SYNTHETIC MEDIUM 199

Ingredients per Liter*

l-Arginine	70.0 mg	Pantothenate	0.01 mg
l-Histidine	20.0 mg	Biotin	0.01 mg
l-Lysine	70.0 mg	Folic Acid	0.01 mg
l-Tyrosine	40.0 mg	Choline	0.50 mg
dl-Tryptophane	20.0 mg	Inositol	0.05 mg
dl-Phenylalanine	50.0 mg	p-Aminobenzoic Acid	0.05 mg
l-Cystine	20.0 mg	Vitamin A	0.10 mg
dl-Methionine	30.0 mg	Calciferol (Vit. D)	0.10 mg
dl-Serine	50.0 mg	Menadione (Vit. K)	0.01 mg
dl-Threonine	60.0 mg	a-Tocopherol Phosphate (Vit. E)	0.01 mg
dl-Leucine	120.0 mg	Ascorbic Acid	0.05 mg
dl-Isoleucine	40.0 mg	Glutathione	0.05 mg
dl-Valine	50.0 mg	Cholesterol	0.2 mg
dl-Glutamic Acid	150.0 mg	Sodium Acetate	50.0 mg
dl-Aspartic Acid	60.0 mg	l-Glutamine	100.0 mg
dl-Alanine	50.0 mg	Adenosinetriphosphate	1.0 mg
l-Proline	40.0 mg	Adenylic Acid	0.2 mg
l-Hydroxyproline	10.0 mg	Iron (as ferric nitrate)	0.1 mg
Glycine	50.0 mg	Ribose	0.5 mg
Cysteine	0.1 mg	Desoxyribose	0.5 mg
Adenine	10.0 mg	Tween 80 (oleic acid)	0.005 mg
Guanine	0.3 mg	Sodium Chloride	8.0 g
Xanthine	0.3 mg	Potassium Chloride	0.4 g
Hypoxanthine	0.3 mg	Calcium Chloride	0.14 g
Thymine	0.3 mg	Magnesium Sulfate	0.2 g
Uracil	0.3 mg	Disodium Phosphate	0.06 g
Thiamin	0.010 mg	Monopotassium phosphate	0.06 g
Riboflavin	0.010 mg	Sodium Bicarbonate	q.s. pH 7.2-7.4
Pyridoxine	0.025 mg		
Pyridoxal	0.025 mg	Dextrose	1.0 g
Niacin	0.025 mg		
Niacinamide	0.025 mg		
Phenol Red	0.02 g		

*Morgan, J. F.; Morton, E. J.; Parker, R. C.: Proc. Soc. Exper. Biol. & Med., 73:1, 1950.

the restoration of volume not only reduce the horse serum content to less than 1 part in 5 million but they also reduce the antibiotic concentrations to minute amounts. By calculation, and without allowing for destruction, deterioration or fixing, the penicillin content is reduced by washing and redilution alone to approximately 0.003 unit per cc, the neomycin content to approximately 0.0000015 mg per cc, and the dihydrostreptomycin content to approximately 0.000003 mg per cc. It is necessary to restore the antibiotic content at the time of virus infection of the cultures so that bacterial contamination can be prevented during the remaining steps in the process.

We formerly added a solution of penicillin G and dihydrostreptomycin to restore the penicillin concentration to 200 units per cc and the dihydrostreptomycin to 0.2 mg per cc. For the past several months, however, we have substituted a solution of polymyxin B and dihydrostreptomycin to bring the final concentration to 50 units of polymyxin B and 0.1 mg of dihyrostreptomycin per cubic centimeter.

The substitution of polymyxin B for penicillin was considered advisable for three reasons:

1. Penicillin biologic (not chemical) assays carried out on finished vaccine when penicillin was added at both points in processing showed a concentration between 1 and 15 units per cc. It is conceivable that this amount of penicillin, albeit small, could induce primary sensitization to penicillin, or cause allergic reactions in persons already extremely sensitive, or both.

It is interesting to note that use of poliomyelitis vaccine containing this amount of penicillin has been compared[2] to the situation wherein horse serum sensitization was produced by the use of toxin-antitoxin mixtures for diphtheria prophylaxis a few decades ago. We are not aware of data substantiating such a comparison but the possibility exists. In this respect, Feinberg[3] has recently reported that the penicillin content of poliomyelitis vaccine he tested was sufficient to produce positive reactions in passively sensitized human skin. He concludes that, although the amount is small, "it is sufficient to produce reactions in highly sensitive persons."

2. The toxic reactions that already have occurred following parenteral administration of polymyxin in therapeutic doses will almost surely prevent wide use of the substance. Because parenteral use of polymyxin is seldom indicated in clinical practice, most persons will never have occasion to receive the drug. In addition, polymyxin is not considered very allergenic. Presumed allergic reactions following its use have been infrequent.[4]

3. Polymyxin has proved a satisfactory replacement for penicillin for prevention of bacterial contamination in the tissue culture system. This point is stressed again because antibiotics are absolutely necessary for mass production of virus fluids. Indeed, if the antibacterial spectrum of polymyxin were not adequate, penicillin or some other agent would have to be used. Replacement of dihydrostreptomycin does not appear necessary. There are data to indicate that 95 per cent of the streptomycin is destroyed in processing. By assay, less than 0.005 mg per milliliter remains in the final product. It is considered that risk of sensitization to this amount is negligible.[5,6]

After inoculation with poliomyelitis virus, the fluids are again incubated at 37 C for a suitable period. The titer of the virus fluids is then determined and the fluids are passed through bacteria-excluding filters. This filtration removes all particulate matter, including monkey erythrocytes, kidney epithelial cells, bacteria and other debris.

The poliomyelitis viruses are inactivated by addition of formaldehyde solution U.S.P. to a final concentration of 1:4000. Following complete inactivation of the individual strain pools, which is determined by extensive testing in tissue culture, the pools are combined in a trivalent mixture. Then, additional tissue culture testing with much larger samples is carried out. The required tests are performed for potency, identity, sterility and the presence of other infectious agents pathogenic for man. If the results of all these tests are satisfactory, the formaldehyde is neutralized with sodium bisulfite and the preservatives are added. A final safety test is carried out, in monkeys, on the contents of vials of finished vaccine selected at random from the filling line.

The preservatives used in Wyeth vaccine are methylparaben and propylparaben in concentrations of 1.5 and 0.2 mg per cc, respectively.

These agents are parahydroxybenzoate derivatives, which have been used as preservatives for millions of doses of penicillin and other parenteral pharmaceuticals. The "parabens" have been found completely satisfactory as preservatives for poliomyelitis vaccine.

In review, then, the essential ingredients include:

1. Medium 199
2. Horse serum in a final concentration of less than 1 part in 5 million
3. Phenolsulfonephthalein, 0.002 per cent
4. Soluble monkey protein, derived from blood or kidney
5. Antibiotics
6. Formaldehyde 1:4000—sodium bisulfite complex
7. Preservatives
8. Poliomyelitis virus protein and nucleoprotein

DISCUSSION

The Salk vaccine has been administered to at least 10 million, and probably more than 15 million, children to date.[7] More than 40 million cc have been released.[8] Most children have received one or two injections, some as many as four. We have not seen or heard of any reports concerning severe anaphylactic reactions. Urticaria, angioneurotic edema, less well defined skin eruptions and mild febrile reactions have been reported.[9-12]

It is obvious that the amino acids and vitamins contained in medium 199 are present in very minute quantities. The amino acids provided by medium 199, which account for much of the total nitrogen content of the final vaccine, are of small molecular size and are probably incapable of sensitization.

The horse serum is present in a concentration calculated at less than one part in 5 million and this calculation does not account for loss by metabolism or destruction. The number of individuals susceptible to primary sensitization by such an infinitesimal amount of horse serum must be few indeed. Furthermore, it is very unlikely that persons already serum-hypersensitive will react following administration of 1/5,000,000 cc, the calculated amount of horse serum contained in a 1 cc dose of poliomyelitis vaccine. Since the amount present is so minute, the National Institutes of Health do not require a label statement concerning the fact that horse serum has been added during processing. The preservatives and antibiotics added after washing and redilution must be declared, however.

Phenol red (phenolsulfonephthalein), which is responsible for the cherry soda color of poliomyelitis vaccine, is added as an indicator so that the pH of the fluids can be followed visually at all times. Phenolsulfonephthalein is present in the vaccine in a concentration of 0.002 per cent. We have been unable to uncover any reports of allergic reactions

to this dye. It is used by urologists and internists in much greater concentrations, but of those I consulted (and I talked to several) none had ever seen or heard of an allergic reaction following use of the substance. The allergenic liability of phenol red, therefore, would appear remote.

To our knowledge, allergic reactions to the preservative, the "parabens," have never been reported.

It has been shown by Horsfall[13] that formaldehyde is capable of causing sensitization. Mansmann[14] and Ratner[15] have shown that allergic reactions to mumps and influenza vaccines, which are inactivated with formaldehyde, may be caused by the formalin content, especially in allergic children. It is recalled, however, that, in poliomyelitis vaccine, the formaldehyde is neutralized by an excess of sodium bisulfite during the later stages of processing.

Several studies have been reported which were carried out specifically to define more clearly the allergenic potential of some of the ingredients.

Naturally, there was concern, and probably some still exists, as to the liability to development of renal damage or sensitization. As reported by Francis[9] and Kumm,[16] Salk and Mayer searched for the development of complement-fixing antibodies against monkey kidney in a series of prevaccination and postvaccination sera collected from individuals who had been given multiple doses of vaccine. In only one was there any suggestion that such antibodies developed, and in this case the findings were of doubtful significance. The child had received vaccine containing adjuvant. Neva and co-workers[17] reported a group of fourteen children who received three or four doses of poliomyelitis vaccine over a period of three months. No evidence of kidney damage or injury could be determined clinically by serial Addis counts and other tests ordinarily used for diagnosis of impaired renal function, including P.S.P. excretion, urine volume and specific gravity, hematologic and chemical determinations. The authors state, "It is of interest to recall that preparations such as liver extract and insulin and several glandular extracts, which also are derived from mammalian organs, have had widespread use and appear not to have produced damage or sensitization in the corresponding organ tissue. Although, under certain conditions, tissues such as central nervous system and testis appear capable of inducing tissue damage directly when administered as antigens, we are unaware of any studies that have shown the production of renal damage in either homologous or heterologous species following injection of kidney tissue suspensions alone. . . . It should be noted that, in studies with central nervous system and testis, as well as in the studies with kidney plus bacterial antigens by the Caveltis, relatively concentrated suspensions of tissue have been used as the antigens to produce organ tissue sensitization. The vaccine currently employed is prepared from fluid derived from cultures of monkey kidney tissue, the cells of which are destroyed by virus cytopathogenic effect; the harvested fluid medium, which is very low in soluble protein,

is further treated by passage through bacteria-tight filters. Thus, any cell or tissue components that might be thought to be capable of producing undesirable effects would have been eliminated or would necessarily be either soluble or of particle size that would be small enough to pass through bacteria-withholding filters. From the above considerations, it would seem unlikely that a vaccine of the kind described could produce renal sensitization, nor, in fact, has it as yet been observed."

Salk also reported that intradermal administration of kidney culture fluids in sixty-four subjects on two or more occasions gave no evidence of dermal sensitivity.[18]

Use of rhesus monkeys as the source of kidney tissue was questioned because of the possibility that repeated injection of Salk vaccine might sensitize the recipient to Rh antigens. Obviously, this could be of serious consequence in Rh-negative females. Francis,[9] in summarizing studies carried out by Milzer and Frisch, states, "Thus, although the data are meager, there is no evidence to date of either kidney damage or Rh sensitization produced by the vaccine." Subsequently, Abelson and associates,[19] after a very extensive study, concluded that the lots of vaccine tested by them did not show even a trace of Rh antigens.

As mentioned previously, the antibiotic content of Salk vaccine has been the subject of most discussion. There appear to be very little pertinent data in the literature to indicate whether or not the "breakdown" products of penicillin are considered allergenic. It is necessary to bring this into the discussion because, even though the starting level of penicillin is approximately 200 units per cc, the final product in the former Wyeth vaccine, when penicillin was added at both points, assayed less than 15 units per cc in all lots tested. The difference between the starting and final levels was either metabolized or it represented deterioration caused by the instability of aqueous penicillin G at incubator temperatures. If one allows a solution of aqueous penicillin to stand without refrigeration until all activity is lost, as determined by biologic assay, is it still antigenic? The data developed by Coleman and Siegel[20] concerning penicillin contamination of sterilizer water or syringes as a cause of allergic reactions in a severely hypersensitive individual leave little doubt that the breakdown products are antigenic. Since polymyxin has been substituted for penicillin during the second phase in processing of the Wyeth virus fluids, the washing and redilution steps previously described reduce the penicillin content, by calculation, to less than 0.003 unit per cc. This does not allow for deterioration or destruction and should include the breakdown products. The number of individuals who are so extremely allergic to penicillin that they would manifest either immediate or delayed reactions to such small doses must be few indeed. This is much less than the dose recommended by Kern,[21] Tuft,[22] Feinberg,[3] and others[23,24] for safe intradermal use in skin testing for penicillin sensitivity, since they suggest injection of 0.01 to 0.02 cc of concentrations varying between 10 and

10,000 units per cc. Nevertheless, it must be remembered that anaphylactic reactions have been reported following injection of extremely small doses. Mayer and co-workers[25] describe a patient who reacted anaphylactically to a test dose of 10 units. The patient reported by Coleman and Siegel[20] reacted anaphylactically to penicillin-contaminated sterilizer water (in which the penicillin content could not be assayed). It was later found, by passive transfer tests using serum of this patient, that 0.00001 unit of penicillin was sufficient to produce a slight positive reaction in the serum-sensitized site of the passive transfer subject.

The possibility of inducing primary sensitization by injection of vaccine containing less than 0.003 unit of penicillin must be considered. It has been pointed out that ingestion of milk from cows recently penicillin-treated for mastitis[3] and use of penicillin-contaminated syringes may constitute primary sensitizing sources of penicillin. Nevertheless, the number of susceptible atopic individuals who may acquire penicillin hypersensitivity from such sources must be very small in comparison to the number sensitized by therapeutic or prophylactic use, judicious or otherwise, of the many dosage forms of penicillin.

Feinberg[3] recently reported, "The amount of penicillin in the poliomyelitis vaccine is small, but, judging by its activity as determined by us in tests of passively sensitized human skin, it is sufficient to produce reactions in highly sensitive persons. However, there do not seem to be reports of severe anaphylactic reactions following injection of the vaccine in the mass immunization programs. These programs have not been carried out on adults, who are probably a more sensitive group."

Siegal[26] came to somewhat different conclusions as a result of a study carried out on allergic adult patients. He states, "Intracutaneous and trial subcutaneous tests with poliomyelitis vaccine in a patient with persistent penicillin sensitivity did not elicit any reaction attributable to its possible penicillin content. Tests in passive transfer sites with the serum of a patient anaphylactically sensitive to penicillin and known to contain a high titer of reagins were also negative, indicating that the penicillin content of poliomyelitis vaccine is negligible. The vaccine should offer no hazard either to persons allergic to penicillin or as a source of newly acquired penicillin sensitization."

Crump has recently reported[11] that, in a series of allergic children tested intradermally with 0.01 to 0.02 cc of poliomyelitis vaccine produced by another manufacturer, positive reactions developed in 50 per cent and 25 per cent of these could be classified as severe. It is not mentioned whether the patients were tested with saline as a control or whether a similar number of normal children were tested. The author recommends that allergic children be skin tested prior to administration of poliomyelitis vaccine and that hyposensitization techniques be carried out in those exhibiting positive reactions. This observation is difficult to correlate with the data reported by Von Magnus.[6] In Denmark during 1955,

425,000 children received two simultaneous intradermal injections of 0.1 to 0.15 cc each of poliomyelitis vaccine prepared by the Salk method. The dose was repeated in four to six weeks. "The reactions following the administration of the vaccine by the dermal route were mild and infrequent, consisting mainly of local swelling of the arm at the site of inoculation. A preliminary estimate indicates that this occurred in 0.1 to 0.2 per cent of the children."[6] Also, there are data suggesting that it is not unusual for children with circulating antibody from prior poliomyelitis virus infection to exhibit a positive reaction when skin-tested with virus fluids. This reaction is manifested by erythema and usually begins to disappear in twenty-four hours.[27] There may be several reasons for the apparent discrepancy in these observations. One is the criterion used for or the definition of a positive skin test. Another could well be the difficulty in interpreting the clinical significance of a positive skin test reaction. Allergists are much more familiar with this problem than I, but the significance of positive reactions occurring in either normal or allergic persons following skin testing with food extracts, vaccines, bacterial extracts and certain other potentially allergenic substances apparently is often difficult to determine.

Except for the Francis report,[9] little data have been published referring to the types of allergic reactions following administration of Salk vaccine. Francis's data show that the incidence of "allergic reactions" was less in the group receiving vaccine than in the group serving as the observed controls. He states, "Some of the skin conditions were defined as urticaria but did not reappear in those given subsequent inoculations with the same material."[9]

We were fortunate in that three of the studies using Wyeth vaccine were carried out in groups of children who could be very carefully observed. These studies involved 939 individuals who received a total of approximately 2,350 injections. Only two reactions were observed which could be considered allergic. Both of these consisted of generalized, nonurticarial rashes which appeared on the fourth to sixth day following injection of the first dose and disappeared in twenty-four hours. Similar reactions did not occur after subsequent inoculations several months later.

It is interesting that in one of these studies the investigator intentionally gave injections of vaccine with the former higher penicillin content to two children with histories of previous delayed, generalized, cutaneous reactions to penicillin. No such reactions followed three separate doses of vaccine administered with intervals of one week between the first and second, and four weeks between the second and third injections. In another patient in this study, a nine-year-old boy, a shocklike state developed immediately after the first injection. The very competent investigator diagnosed "too much bravery" and "lack of breakfast" as the causes.[28] She apparently proved her point when, at the time of the second and third injections, there were less anxiety and a full stomach, and no untoward

reaction occurred. I mention this merely to emphasize that it is common procedure to blame all occurrences following the injection of a new agent ON the agent. It is obvious that, with a less responsible and alert investigator, this could readily have been called an anaphylactoid reaction to poliomyelitis vaccine. It also must be remembered that almost every type of side effect and toxic reaction, including allergic responses, has been reported following oral and parenteral double blind administration of placebos[29,30] and that positive skin test reactions to saline in both normal and allergic individuals have been reported.[31,32]

SUMMARY AND CONCLUSIONS

Allergic reactions following administration of poliomyelitis vaccine prepared and tested as described are to be expected in a very small percentage of cases. All available data so far indicate that the allergic reaction rate compares favorably with that of other refined biologic products. Only continued widespread use will determine the potential allergenicity of the vaccine with regard to both primary sensitization and causation of reactions in those already hypersensitive to one or more of the ingredients.

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Thus history teaches us that any division of the science and the art of medicine is necessarily harmful to practice. The physician of today, better realizing the limitations of bacteriological and other technical aids, is experiencing the need of returning to the patient's bedside, from which medicine should never have separated itself. With the extreme swing of the pendulum too much faith has sometimes been placed on the pronouncements of the laboratory when, forgetting the importance of the clinical picture, physicians have based their activities too exclusively on laboratory criteria. For some years now physicians have tended through ignorance of the possibilities and limitations of laboratory methods either to place too much reliance on what came out of the four walls of the laboratory, or not to take advantage of the information that it could properly give. They tended to pay more attention to the evidence of the microscope and chemical reagents than to information obtained by their own senses from examination of the patients in the wards of the hospitals.—ARTURO CASTIGLIONI (1874-)—*A History of Medicine.*

PNEUMONITIS AND ATELECTASIS OCCURRING IN THE COURSE OF ALLERGIC DISEASE

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and
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IN the past, while treating patients with extrinsic bronchial asthma, we became aware that some of our patients suddenly developed pyrexia, cough, wheezing, and dyspnea, symptoms which did not appear to have any direct relation to their allergic disease. Examination of each of these patients revealed that they all had a pneumonitis of the middle lobe with some associated atelectasis of this lobe. They were treated with antibiotics with favorable results.

Since 1848 we have recognized this to be the classic middle lobe syndrome described by Graham et al.[3] With the recognition of this syndrome, treatment was changed to include medication to alleviate the bronchial obstruction, in addition to adequate doses of the antibiotics. The morbidity of this disease has decreased with the inception of this regimen.

The syndrome of collapse of the middle lobe was described by Brock in 1943 and 1946.[1] He postulated that the collapse was due to pressure of healed tuberculous glands around the middle lobe bronchus. In 1950, Brock[2] described sixty cases of this symptom complex, all of which were due to active and healed tuberculous lymphadenitis, and he discussed the pathology and mechanism of this syndrome.

Paulson and Chaw[4] in 1949 described thirty-two patients with collapse of the middle lobe, persisting from five months to twenty years, and twenty-nine of them had middle lobe pneumonectomy. In the majority of these patients, the disease was found to be caused by inflammation and edema of the bronchial wall, as well as adjacent inflamed lymph glands.

Graham et al[3] in 1948 described one case of the middle lobe syndrome of six years' duration, which was also treated surgically.

In the cases we wish to report, none required surgical intervention. All our cases were of the acute type, and we feel that early medical treatment prevented this syndrome from becoming chronic; the chronicity apparently leads to surgical intervention.

CASE REPORTS

Case 1.—P. S., a woman, aged fifty-one, was seen in April, 1949, because of a history of cough and nasal symptoms since 1943. The symptoms came in "attacks," and when the attacks were over she was well. She lived on a farm, and had cats and dogs in the house. Her nose revealed a typical allergic appearance on

From the Asthma and Hay Fever Clinic, Cleveland, Ohio.

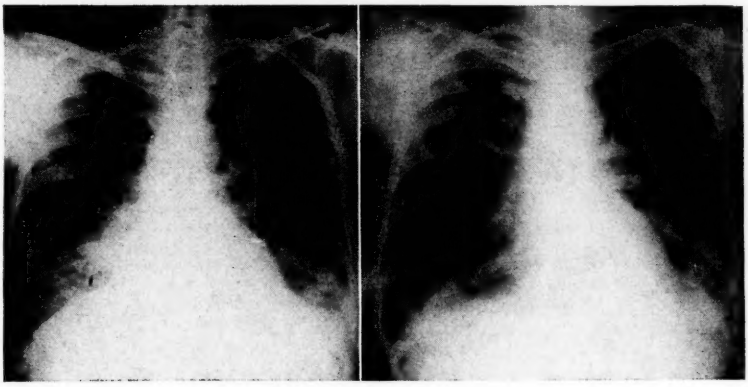

Fig. 1. Patient P. S. showing infiltration in middle lobe segment.
Fig. 2. Patient P. S. showing almost complete clearing of previous infiltration.

physical examination. Her chest was only slightly emphysematous and was filled with rhonchi, but no expiratory wheezing was present. She gave positive intradermal tests to dust, grass and ragweed pollen, and to dog and cat danders.

Treatment was instituted, and she did fairly well until August 13, 1949, at which time she stated that for about a week she had had cough and bronchial asthma, with dyspnea but no orthopnea. A slight hemoptysis was noted. Examination revealed emphysema and roles in both bases with expiratory wheezes in both lung fields. Fluoroscopy of the chest revealed a right triangular area of infiltration in the right lower lung field. Roentgenographic examination of the chest showed this area of infiltration to be in the middle lobe, associated with collapse of the middle lobe segment (Fig. 1). She was placed on antibiotics (penicillin) and an expectorant mixture of ephedrine, potassium iodide, and apomorphine. On September 3, 1949, the chest x-ray (Fig. 2) was clear, but the patient was still having same symptoms as well as signs of bronchial obstruction. She was last seen on March 14, 1952, at which time she was having no asthmatic symptoms, and the chest x-ray showed no evidence of pulmonary infiltration. She discontinued her desensitization therapy at this time.

Case 2.—R. K., a nine-year-old boy, was first seen in October, 1949, because of winter cough and wheezing. From his first year of life this boy had had what was called "winter bronchitis," as the cough never was present in the summer. The current attack of wheezing began October 1, 1949, and his last previous attack had been in March, 1949.

Physical examination revealed a child with poor posture and muscle tone, and definite facial stigmata of allergy. The nasal mucosa was pale and boggy, and extensive edema of the middle turbinates was noted. The chest cage was emphysematous and there were many sonorous rales throughout the lung fields. The fluoroscopic examination was not remarkable except for increased bronchial markings. Skin tests were positive to house dust; therefore, adequate house dust precautions were instituted, and the patient was desensitized with house dust.

The boy did very well until November 22, 1949, when he presented himself because of wheezing and pyrexia. Physical examination revealed a cyanotic youngster with dyspnea and audible wheezing. There were sonorous rales throughout the lung fields. The white blood count was 18,700; polymorphonuclears, 87; lympho-

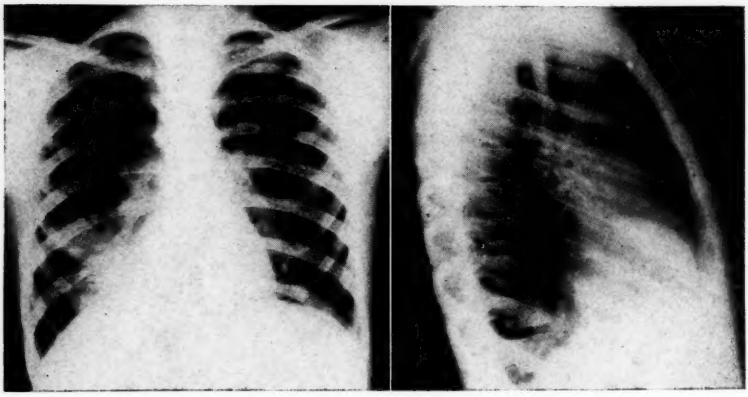

Fig. 3 (a and b). Patient R. K. showing infiltration of middle lobe with collapse of the middle lobe segment.

cytes, 12; and monocytes, 1. X-ray of the chest showed a triangular infiltration of the right lower lung field and an area of increased density in the sixth interspace, limited by the interlobar fissure. A right lateral showed the infiltration to be in the middle lobe and associated with the collapse of the middle lobe segment (Fig. 3, a and b). This patient was treated with antibiotics, ephedrine, potassium iodide, and with 3¼ gr aminophylline rectally at bedtime.

By November 29, 1949, an x-ray of the chest showed marked diminishing of the infiltrate in the right middle lobe, with the re-expansion of the middle lobe segment (Fig. 4, a and b). With allergic management and desensitization, this patient did extremely well. His bouts of bronchitis subsided, and in 1953, after one year of relative freedom from all difficulty, he was discharged. We have heard that his condition remains good.

Case 3.—L. B. was first seen in April, 1950, at the age of fifty-three years, because of perennial wheezing which had begun at age fifty-one. The attacks began a few months after a cat was introduced into the home.

Physical examination revealed a rather marked kyphosis and some coarse expiratory rhonchi over the lower half of the chest posteriorly. Skin tests were positive to cat danders, dust, feathers, and ragweed pollen. Dust and feather precautions were ordered along with cat avoidance. This patient responded well to desensitization therapy.

In June, 1955, while on her periodic holiday from desensitization therapy, she developed an upper respiratory infection with cough and was given penicillin by her family physician. She was seen two weeks later, June 24, 1955, at our office because she had not improved. Physical examination revealed marked emphysema, rales and rhonchi in both lung fields. Fluoroscopy revealed an infiltration in the middle lobe with collapse of the middle lobe segment. An x-ray examination confirmed the findings.

The patient responded well to treatment with intravenous and rectal aminophylline and to the use of antibiotic therapy, bronchidilators and expectorants. In three weeks, July 18, 1955, the lesion in the middle lobe was clear, and the patient has continued to do well since.

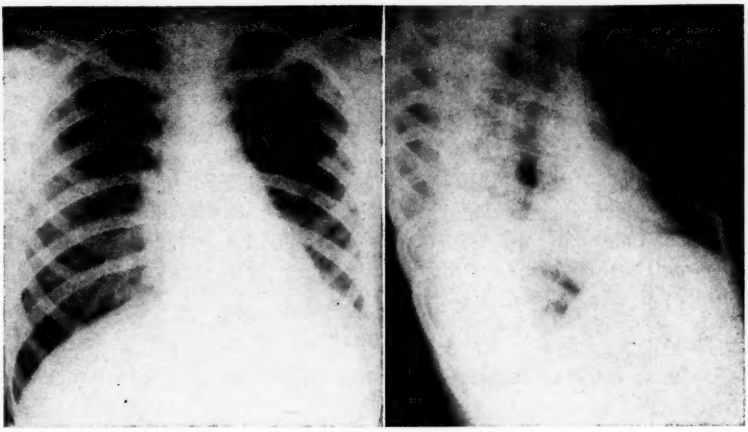

Fig. 4 (a and b). Patient R. K. showing complete clearing of previous involvement, seven days later.

Case 4.—M. A., a fifty-nine-year-old male, gave a history of having had rhinorrhea with nasal obstruction for fifteen or eighteen years. Four years before his first visit on August 20, 1955, he began having attacks of coughing, wheezing, and hemoptysis. In July, 1955, a few weeks after his return from Florida, he developed shortness of breath with wheezing.

The chest revealed marked emphysema with distant breath sounds and some rhonchi and expiratory wheezes. The heart sounds were distant and irregular. X-ray examination of the chest revealed cardiac enlargement and an area of infiltration in the middle lobe segment with partial collapse of the middle lobe segment. Skin tests were positive to house dust, feathers, alternaria, and ragweed pollen. House dust and feather precautions were instituted, and desensitization therapy with house dust, ragweed pollen and alternaria was started.

The infiltration and collapse of the middle lobe was managed with antibiotics, bronchodilators and expectorants. An x-ray examination sixteen days later, September 9, 1955, showed clearing of the infiltrate described above, except for some pleural scarring.

DISCUSSION

We feel that the important factor in this disease is its early recognition and treatment. This eliminates the later complication of a permanent type of atelectasis and bronchiectasis, requiring surgical removel of the involved lung segment.

In our cases, the onset was acute and, since we were aware of this disease, the patients were given prompt treatment with antibiotics, expectorants, and bronchodilators. Usually, the expectorants used were potassium iodide and/or apomorphine hydrochloride.

The histories presented were all of allergic patients, and we feel that the mechanism of the collapse was due to bronchial allergy and its resulting inspissated mucus occluding the bronchioles, followed by secondary

infection and producing a complete obstruction of the smaller air passageways. The relief of the edema and bronchiolar obstructions gave gratifying results to our patients and, when the infection was also controlled by the use of proper antibiotics, recovery was prompt and complete.

We feel that bronchoscopy and surgical intervention in such cases as described above is not warranted, because early medical management gives uniformly good results. We have followed these cases for a considerable length of time and none of them has developed bronchiogenic carcinoma or chronic infections of the middle lobe.

SUMMARY

1. Four cases of middle lobe syndrome in allergic patients are reported.
2. Therapy in these cases includes bronchodilator drugs and antibiotics.
3. Early recognition and treatment of this syndrome are important for complete recovery.
4. An etiology of this syndrome is postulated for our patients.

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There was one quality of mind which seemed to be of special and extreme advantage in leading him to make discoveries. It was the power of never letting exceptions pass unnoticed. Everybody notices a fact as an exception when it is striking or frequent, but he had a special instinct for arresting an exception. A point apparently slight and unconnected with his present work is passed over by many a man almost unconsciously with some half-considered explanation which is in fact no explanation. It was these things that he seized on to make a start from. In a certain sense there is nothing special in this procedure, many discoveries being made by means of it. I only mention it because as I watched him work, the value of this power to an experimenter was so strongly impressed upon me.—Francis Darwin (1848-1925) —*Autobiography (about his father).*

THE TREATMENT OF ALLERGIC DISEASES WITH THE STEROID HORMONES

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A SURVEY was made of 417 patients with various allergic disturbances who received as primary treatment, parenteral, oral, and local steroid hormones. The voluminous literature in the use of these hormones over the last five years, attesting to the favorable results obtained in the production of remissions of allergic diseases, places them in a primary position in our therapeutic armamentarium of allergic management. Our series of cases treated privately in the office and in the hospital over a period of three years includes 102 cases of bronchial asthma, 113 cases of contact dermatitis, seventy-three cases of atopic eczema, forty-seven cases of inhalant allergies (or allergic rhinitis), seventy-two cases of acute and chronic urticaria and drug reactions, and ten cases of poison ivy. These cases were selected as follows:

1. The acute allergic emergencies, previously not treated at all or treated by others without satisfactory results.
2. Those acute or subacute allergic patients to whom we wished to give rapid relief prior to *careful allergic workup*. (One temporary relief was obtained, these patients were placed on allergic management only.)
3. Those allergic patients who had been on allergic management alone, or allergic management plus conventional therapy, without obtaining satisfactory relief.
4. As a supplement to allerigc management where partial relief had been obtained and where relapses were not controlled by conventional therapy.
5. In acute allergic skin disorders where conventional therapy required prolonged treatment and where it was desirous to get patients back to work rapidly for economic reasons.

Our purpose in this report is to evaluate and document the results of treatment in each of these several categories and to report such side reactions and sequelae as may have occurred. Parenteral ACTH was the drug of choice in 95 per cent of these cases, both the aqueous and the gelatin solutions being used. Hydrocortone ointment in 2.5 per cent strength was used topically in the dermatologic cases.

METHODS OF TREATMENT

In the several cases of status asthmaticus, the patients were hospitalized and given aqueous ACTH in doses of 20 units per 500 cc of 5 per cent

Presented before the International Association of Allergists at Rio de Janeiro, Brazil, November 11, 1955.

glucose in water. The dose varied from 20 to 80 units in twenty-four hours, depending upon the age and the condition of the patient and the response to treatment. This was given at the rate of twenty-five to forty drops a minute. The only other drugs, in addition to oxygen, were rectal Nembutal® or Seconal® for restlessness, digitalis in various dosages for associated decompensated heart disease, and potassium chloride, 15 to 30 grains daily. Following initial favorable response to the intravenous medication, ACTH was given intramuscularly in from 80 to 160 units daily for another twenty-four to forty-eight hours. Then, the parenteral use of the drug was greatly reduced or discontinued, and the patient was placed on the oral medication of steroids. Until two and one half years ago, Cortone® in daily doses of 20 to 100 mg was employed. In the past six months, Meticortone® or Meticortelone® in doses of 5 to 20 mg was used daily every other day or only one or two times a week, the dose being adjusted to the patient's clinical status. Vital capacity changes, blood pressure fluctuations, blood sugars, and blood chlorides were carefully observed on each patient during the patient's hospital stay and from once a week to once a month while the patient was on ambulatory treatment with the oral medication.

In the ambulatory type of bronchial asthma, cases which were responding poorly or not at all to the usual drug therapy, ACTH in doses ranging from 20 to 80 units of aqueous material were administered daily in the office, and as improvement occurred, ACTH, in gel, was substituted in doses of 80 to 160 units every other day to once or twice weekly. Such parenteral treatment was carried out in spite of the muscular soreness or local reactions which often occur with parenteral injections, because, after initial trial and error, it was felt these patients had not responded sufficiently to oral medication alone even in large doses. Following parenteral therapy of hours to days, where improvement did occur, the parenteral treatment was followed by the oral Cortone in doses of 20 to 60 units a day at the outset, with a gradual reduction to 20 units daily every other day, or as infrequently as two or three times a week. More recently, with Meticortelone and Meticortone, we have been able to reduce the oral dosage by one-half to two-thirds of the amount of Cortone. In the few instances where reactions or intolerance to ACTH occurred at the onset of treatment, cortisone in 100 to 400 mm daily dosage was substituted, followed by the aforementioned treatment with the oral steroids.

In the group of patients with status asthmaticus, treatment was carried on as long as two and one half years with only occasional relapses. These remissive cases responded to daily or biweekly intramuscular injections of ACTH with the gradual substitution of oral steroids. Only seven of these patients, six of whom were over the age of fifty, required rehospitalization following acute upper respiratory infections. The detailed results of treatment in the asthma group are shown in Table I.

TABLE I. RESULTS OF TREATMENT IN 102 BRONCHIAL ASTHMA CASES

Ages	Sex		Av. Duration of Disease	Prev. Allergic Management Alone	Conventional Treatment	Response to Prev. Treatment	Response to Steroid Treatment
	M	F					
0-10 (23)	10	13	2 yrs. 7 mo.	8	16	Good—2 Fair—8 Poor—10 No prev. treatment 3	Good—15 Fair—7 Poor—1
10-30 (16)	6	10	5.6 yrs.	6	10	Good—5 Fair—5 Poor—6	Good—12 Fair—4 Poor—0
30-50 (26)	6	20	8.8 yrs.	8	18	Good—2 Fair—11 Poor—11 No prev. treatment 2	Good—11 Fair—8 Poor—7
Over 50 (37)	11	26	16.7 yrs.	13	24	Good—5 Fair—11 Poor—21	Good—25 Fair—10 Poor—2
Totals (102)	33	69		35	68	Good—14 Fair—35 Poor—48	Good—63 Fair—29 Poor—10

In the treatment of those patients with acute urticaria, drug reactions, and poison ivy dermatitis who were hospitalized, aqueous ACTH in 20 to 40 unit doses by intravenous drip was used for the first twenty-four hours in the manner previously described in the treatment of those with asthma. Within a period of hours, most of these patients were so much improved that intramuscular treatment was instituted for the remainder of the hospital stay, followed by oral steroids where necessary. The dosage again varied according to the severity of the condition and the rapidity of the response to intravenous medication. In addition to the parenteral ACTH and oral steroids (20 to 60 units a day), hydrocortone ointment, 2½ per cent, was prescribed for local application.

The treatment of ambulatory patients with contact dermatitis and acute and chronic urticarias consisted of initial injections of 80 to 160 units of aqueous ACTH for the first twenty-four to seventy-two hours, followed by gradually reduced amounts of the ACTH, in gel, until improvement warranted change to oral medication. Tablets of oral steroids (Meticortone in the past six months) units 20 to 40, were then given at intervals of every one to three days until recovery or improvement was sufficient to warrant withdrawal of the drug. This varied from a few days to several weeks.

Additional treatment consisted of removal of the sources of the offending factors, bandaging in atopic eczema, plus changes of jobs, improved hygiene, et cetera. Where many of these cases were of an allergic background, they were switched over to allergic investigation and management following recovery or improvement with the steroids.

The treatment of the inhalant allergy patients who did not respond satisfactorily to conventional treatment, i.e., antihistamines, allergic management, et cetera, consisted of parenteral injections of aqueous ACTH

in dosage of 20 to 120 units of regular aqueous ACTH for the first twenty-four to forty-eight hours depending upon the age, weight, and the severity of the symptoms. Following this, ACTH in gel was substituted in dosages of from 80 to 160 units every other day or twice weekly until such time as the acute symptoms subsided. Then, the patient's dosage was gradually reduced and the patient was placed on oral steroids. In addition, inhalant nasal sprays of 1 per cent hydrocortone were prescribed one to four times daily. All of these patients were ambulatory.

TABLE I. RESPONSE OF 102 ASTHMATIC PATIENTS TO ACTH OVER THREE-YEAR PERIOD

Good—63 with average remissions of 9.4 weeks	
Fair— 29 with remissions averaging 2 weeks, 5 days	
Poor— 10	
Side Reactions or Sequelae	
Mooning	5
Edema of Extremities	2
Acne	1
Hirsutism	0
Syncope	0
Dizziness	1
Headaches	0
Hypertension	0
Diabetes	0
Urticaria	0
Cerebral symptoms	0
Excessive weight gain	2
Total	11

RESULTS OF TREATMENT—BRONCHIAL ASTHMA SERIES

In this series of 102 patients, there were thirty-three males and sixty-nine females, ranging in age from two months to eighty-eight years. Thirty-two patients had been under previous allergic management in addition to drug therapy (but no steroids), and seventy patients had received the conventional drug therapy. Twelve patients had shown good responses to the allergic management plus conventional drug therapy, with average remissions of five and one half weeks in a treatment period of one to one and one half years. However, because of increasingly recurring attacks of asthma, it was felt worthwhile to make a trial with the steroids. Thirty-nine of the 102 asthmatic patients had fair relief with conventional drug therapy, with persistence of cough and dyspnea, but with remissions from the wheezing for intervals of a few hours to six days. Forty-five patients had poor results from the conventional drug treatment. The response of these same 102 patients with asthma to ACTH over a three-year period is as follows. Good—63, with average remissions of 9.4 weeks; fair—29, with remissions averaging 2 weeks, 5 days; and poor—10.

Nine out of the ten listed as "poor" were over fifty years of age. Forty-two of the 102 patients have been maintained on allergic management plus drug and/or ACTH treatment for the past one and one half years. Eleven side reactions occurred, but gradually subsided when oral steroids were substituted.

TABLE II. ALLERGIC RHINITIS

(Inhalant Allergies)

Number of Patients treated with Steroids —47			
Ages		*Sex*	
5-15	(8)	Males —17	
15-30	(6)	Females —30	
30-50	(26)		
Over 50	(7)		
Number previously treated	28		
Drug Therapy Only	15		
Allergic Management Only	4		
Allergic Management Plus drug therapy	9		
Number Not Previously Treated	19		
Results of Steroid Treatment		Results of Previous Drug Treatment	
Complete relief —21 (3.5 days average time)		Complete relief — 0	
Partial relief —16 (5 days average time)		Partial relief —13	
No relief —10 (10 days average time)		No relief —34	
Average total dose of ACTH per patient—175 Units			
Side Reactions—0			

TABLE III. CONTACT DERMATITIS

Steroid Treatment		Previous Conventional Drug Therapy
Total Number of Cases	113	37
Sex: Male—53 Female—60		
Average duration of symptoms	183 days	
Average duration of treatment with ACTH	10.8 days	24.5 days
Number with positive patch tests	84	
Complete Remissions	68	0
Partial Relief of Symptoms	34	31
No Relief of Symptoms	11	82
Recurrence of lesions after cessation of treatment	16	
Average total dose of steroid per patient (parenteral)	ACTH 237 units	

Side Reactions or Sequelae

Mooning	4	Syncope	1	Diabetes	0
Edema of extremities	3	Dizziness	1	Urticaria	0
Acne	1	Headaches	2	Cerebral symptoms	0
Hirsutism	0	Hypertension	0	Total	12

TABLE IV. ATOPIC ECZEMA

Number of Patients	73
Age Range	6 weeks to 73 years
Sex	Males—35, Females—38
Average Duration of Disease—7.4 months (varying from 3 weeks to 18 years)	
Previous Treatment	38
Remissions with Previous Drug or Allergic Management	24
Average Duration of Remissions	17 days
No Remissions with Previous Treatment	14
Remissions with Steroids	64
Average Duration of Remissions with Steroid Therapy	36.5 days
Stopped Treatment	9
Now on Allergic Management plus Steroids	32

Side Reactions

Mooning	2	Hypertension	1	
Edema of extremities	2	Diabetes	0	
Acne	1	Urticaria	2	(Cleared when patient
Hirsutism	0	Cerebral symptoms	0	was treated with Cortisone)
Syncope	0	Vaginal bleeding	1	
Dizziness	0			
Headaches	0	Total	9	

RESULTS OF TREATMENT—INHALANT ALLERGIES (OR ALLERGIC RHINITIS)

There were forty-seven patients, seventeen males and thirty females, ranging in age from five to seventy-one years, in this group. Of this number, twenty-eight had previously been treated for colds without response to treatment. Fifteen had received only drug therapy, four had allergic management only, and nine had been given allergic management plus drug therapy; nineteen had not received previous treatment. In all of the above cases, the symptoms were so severe and intractable that steroid treatment was indicated as a last resort. All had received allergy tests and were placed on allergic management alone or along with the conventional drugs as soon as their symptoms were controlled by the steroids. Results of hormone treatment in these cases reveal that twenty-one obtained complete relief in an average duration of three and one half days, sixteen obtained partial relief in an average of five days, and ten obtained no relief over a ten-day-period of treatment. The average total dose per patient was 175 units of ACTH. There were no side reactions in this group. Oral steroids alone were tried in the beginning but, because the initial response to treatment was not satisfactory, the medication was given parenterally for the first few doses. A rapid response usually occurred; then maintenance doses of oral steroids

TABLE V. URTICARIA

Total Number of Patients		72
Acute Urticaria	58	
Penicillin Reactions—	8	
Other Drug Reactions—	9	
Other Causes—	41	
Chronic Urticaria	14	
Age Range: 16 months to 76 years		
ACTH Treated	66	
Cortisone Treated	6	

Average total dose (ACTH) for 66 patients—145 Units
Average total dose for Cortisone treated patients (6)—850 Units

Average Recovery Time		*Side Reactions*
Acute Urticarias	2.5 days	None in acute patients
Chronic Urticarias	3 months	3 in chronic patients
Not recovered—2		Mooning —2
Remissions —3		Edema —1

were sufficient to control symptoms. Again, let me emphasize that all of these patients were placed on allergic management as soon as was practically possible.

RESULTS OF TREATMENT OF CONTACT DERMATITIS, ATOPIC ECZEMA, ACUTE AND CHRONIC URTICARIA

Tables III, IV, and V list the results of treatment in the above-named conditions. Of the 113 patients with contact dermatitis, sixty-eight had complete remissions, thirty-four had only partial relief of the symptoms, eleven (9 per cent) obtained no relief in spite of being removed from the sources of irritation, in some cases from their jobs, and despite persistent treatment over periods of months with bandaging, drugs, et cetera; sixteen (14 per cent) had a recurrence of the lesions and symptoms after the cessation treatment and required intermittent parenteral ACTH and oral steroids for periods of weeks to months. Four are still under treatment at the present time.

The average total dose of the hormone ACTH was 237 units per patient. Side reactions and sequelae numbered fourteen, or twelve per cent. One patient, a twenty-seven-year-old female, had vaginal bleeding after she had about 600 units of ACTH.

Of the seventy-three patients with atopic eczema, whose ages ranged from six weeks to seventy-three years, the average duration of the disease was 7.4 months (varying from three weeks to eighteen years). Thirty-eight had had previous drug treatment prior to coming to our office. Of the thirty-eight, twenty-four had had some remissions with the previous drug or allergic management, with an average duration of seventeen days for their remissions. Fourteen had obtained no remissions with the previous drug therapy. Of the ACTH—or cortisone—

TABLE VI. POISON IVY DERMATITIS

Number of Patients	10
Age Range	8 to 36
Sex: Males—4, Females—6	
Average Duration of Lesions and Symptoms before treatment—	3.5 days
Average Duration of Treatment with ACTH with complete recovery—	3.1 days
Average Dosage of ACTH per patient	206 Units

Side Reactions: None

treated patients, sixty-four (80 per cent), had remissions for an average of 36.5 days, nine stopped treatment, and thirty-two are at present under allergic management plus hormone treatment.

Side reactions occurred in 9 per cent of the patients, two of whom, one male and one female, developed severe urticaria following the second and third injections of ACTH, respectively. These symptoms subsided with large parenteral doses of cortisone.

In the urticarial group of seventy-two patients, ranging in age from sixteen months to seventy-six years, fifty-eight had acute urticaria or angioedema, and fourteen had chronic urticaria. Of these, sixty-six were treated with ACTH and six with cortisone. The average total dose of ACTH was 145 units, 850 units of cortisone. The average recovery time in the acute cases was two and one half days, and 3 months for those with chronic urticaria. Two of the chronic urticarial patients have shown no evidence of recovery, and three have relapsed. There were no side reactions in the acute urticarial cases and three in the chronic urticarial group.

In the poison ivy series there were ten patients, of whom four were males and six were females, with an average duration of lesions and symptoms before treatment of three and one half days. The average duration of recovery with ACTH-treated patients was 3.1 days, the average dosage of ACTH per patient was 206 units, and there were no side reactions.

DISCUSSION

By now, we recognize fairly well the limitations and pitfalls in the treatment of allergic diseases with steroid hormones and that their value as a symptomatic weapon only, but not as a cure, is a little less than spectacular. Let it be understood again and strongly emphasized that all of these patients, with the exception of those with poison ivy, were those who had not responded or had responded poorly to allergic or conventional treatments, who had not been treated at all, or who required heroic and immediate treatment. In our hands, allergic management has always been, and still is, the treatment of choice; however, the steroids

TABLE VII. SUMMARY

Total Number of Patients Treated			417
Ambulatory treated	339		
Hospitalized	78		
Response to Treatment	No.	Per Cent	
Good	283	67.6	
Fair	79	18.9	
Poor	45	15.5	
Side Reactions	36	8.0	No Fatalities

remain the best stopgap treatment to date. Each patient who received the steroids was informed that this was a treatment for the symptoms only and was not intended as a complete cure, and where possible, they would be placed on, or continued on, allergic management after their acute symptoms were under control.

The economic factor was important in this series of cases. A large majority of these people were of very limited means and were not always equipped with hospital insurance and could ill afford prolonged hospital care. Furthermore, a large majority of these patients were ambulatory and could best be treated in the office while continuing in their various employments in this industrial community. A few patients with status asthmaticus, acute urticaria, and weeping dermatoses were hospitalized. These were placed on ambulatory treatment as soon as the acute symptoms were controlled.

SUMMARY

Four hundred seventeen patients with various allergic disturbances were treated over a period of three years with the steroid hormones by parenteral, oral, and local means. All were on ambulatory treatment, except seventy-eight of this group who required hospitalization for intervals of one to seventeen days. Thereafter, these were placed on ambulatory treatment except for several periods of relapses each (for the patients with status asthmaticus).

Of the total number, 283 (67.6 per cent) had good response to treatment; seventy-nine (18.9 per cent) had fair response; and 45 (13.5 per cent) had poor or unsatisfactory results. In other words, 362 (86.5 per cent) obtained a considerable degree of relief.

Side reactions occurred in thirty-six (8 per cent) of the patients, with recovery in all following cessation of parenteral treatment.

CONCLUSIONS

1. After careful allergic management itself, the steroid hormones have proved to be a primary adjunct in the relief of a certain percentage of allergic diseases.

2. The steroids have given symptomatic relief in certain patients who

have failed to respond to allergic management alone or to allergic treatment plus conventional drug therapy.

3. The steroids have given symptomatic relief to patients prior to and in preparation for allergic management.

4. In our hands, parenteral hormone therapy has given more rapid relief of symptoms in status asthmaticus, acute urticaria, drug reactions, poison ivy dermatitis, acute atopic and contact dermatitis, than any other conventional drug therapy to date.

5. Oral steroid hormones have not proved as efficient as the parenteral therapy in the initial treatment of symptoms, but have been valuable maintenance therapy until allergic management alone or allergic management plus conventional drug therapy could be instituted.

6. Side reactions and sequelae have been sufficiently frequent and severe as to limit the use of steroids to those patients which need immediate relief from acute and severe symptoms not controlled by allergic management alone or plus conventional drugs.

7. Careful observations of all patients under steroid therapy should be maintained at all times.

8. There have been no deaths in our series of patients while under treatment with the steroids, and all side reactions and sequelae ceased with withdrawal of the hormone.

9. Steroid therapy treats symptoms only and should not be substituted for good allergic management.

625-57th Street
Submitted March 27, 1956

When a man sets to work to study one of the natural sciences, he provides himself with forms of thought, mental images, which may be called the principles of that science. The chemist has mental images of atoms combining or separating, under definite laws, with definite results: the geologist has mental images of an earth cooled through millions of years from a red-hot haze of gases to a hard globe, and cracked in the cooling. Other men of science, the botanist, the bacteriologist, the physiologist, have mental images of living matter. Is there any difference in kind, between the mental images of chemistry and those of physiology? Surely, there is no such difference. Matter is none the less matter, though it be living: and motion is none the less motion, though it be voluntary.—WALTER PAGET (1855-1926)—*Confessio Medici.*

PSYCHOGENIC ECZEMA IN A CHILD

Report of a Case

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ONE of the important questions to be answered by the allergist today concerns the role of emotional tensions in intensifying or producing childhood eczema. This has been repeatedly emphasized in recent years by reports from qualified allergists that elimination diets based upon carefully performed skin tests for allergic hypersensitivity did not always result in amelioration of the eczema in accordance with the immunologic theory of eczema. I believe that the problem has less to do with establishing that all eczemas are basically allergic and more to do with the determination of how important psychologic forces are in producing or maintaining childhood eczema not responding to immunologically directed therapy.

This is a report of a case in which: (1) the psychologic factors are clear cut, (2) the origin of the eczema is specifically connected with these psychologic factors, and (3) therapy based upon the understanding of these factors resulted in curing the child of eczema for prolonged periods.

Betty, age four-and-a-half, was first seen by me on September 12, 1952. She was one of two children, and her brother, six years older, shared a bedroom with her. When she was seventeen months old she started to withhold her bowel movements for periods of time, sometimes lasting as long as ten days. The family physician regarded this as a behavior problem, but this retention of stools led to two series of barium enemas, which were negative, and eczema developed on the creases of the buttocks and behind the knees. The child had been taken to a series of physicians who had explored the eczema from the point of view of allergy, dermatology, and, possibly psychiatry. When Betty first came to me, the eczema had been present for fifteen months. The mother reported that, although Betty was a healthy child, "She screamed all the time for the first six months of her first year. In order not to hear her cry, we would go into the shower." She was a demanding child, and the mother gave her whatever she demanded. She had no allergic symptoms, and the family history was also negative.

Over a period of one month psychotherapeutic interviews were held with the child, based on the drawings shown in the four figures. Figure 1 (right), the first drawing the child made, is a series of concentric circles with an elaborate border. In Figure 1 (left) there are two series of concentric circles, with some plus signs and little circles between the plus signs which Betty said were her "secrets." Some of the more striking points of the interview are included in the figure. A summary from my notes covers some of these important points.

Therapist: "What's in the writing?"

Betty: "I don't want to tell."

Presented at the Eleventh Annual Congress of the American College of Allergists, April 28, 1955, Chicago, Illinois.

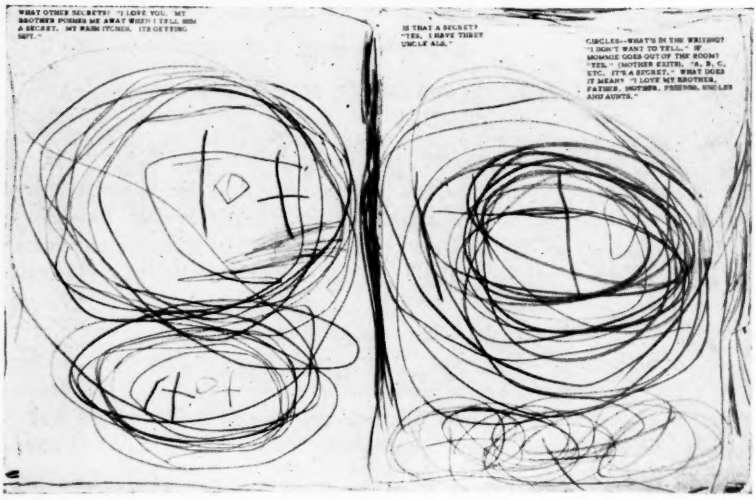

Fig. 1

Therapist: "Will you tell me if Mommie goes out of the room?"
Betty: "Yes."
(The mother left the room).
Therapist: "Do you want to tell me now?"
Betty: "A, B, C, D, E, F, G, et cetera. It's a secret."
Therapist: "What does it mean?"
Betty: "I love my brother, father, mother, friends, uncles, and aunts."
Therapist: "Is that a secret?"
Betty: "Yes. I have three uncle Als."
The patient then drew the second circle, to the left, and the discussion resumed.
Therapist: "What other secrets do you want to tell me?"
Betty: "I love you. *My brother pushes me away when I tell him a secret. My rash itches. It's getting hot.*"

At this time Betty showed a great deal of disturbance, became anxious, started to scratch, and rushed out of the room to see her mother.

On the basis of the first interview a tentative diagnosis was made that some traumatic incident, possibly an accidental seduction involving her brother, occurred when Betty was about seventeen months old. The mother was strongly urged to give her a separate room. It became clear that the withholding of the bowel movements, the barium enemas, and the appearance of the eczema could be connected as a series of emotionally traumatic incidents. I prescribed Bacitracin® ointment and Phenergan® at night to relieve the eczema.

In a second psychotherapeutic session with Betty, again utilizing drawings, the confusion in the original drawings was replaced by a more orderly pattern showing a similar arrangement of circles, but somewhat changed (Fig. 2). Betty interpreted the diagram on the right as: "These are my secrets. I love my mother, father, brother so much. *I hope they don't die. My brother kisses me and hugs me. He plays show with me.* We make a fort. He reads me stories. He dresses me and thinks I'm a baby. My mother and father dress me. They all feed me. They think I'm a baby."

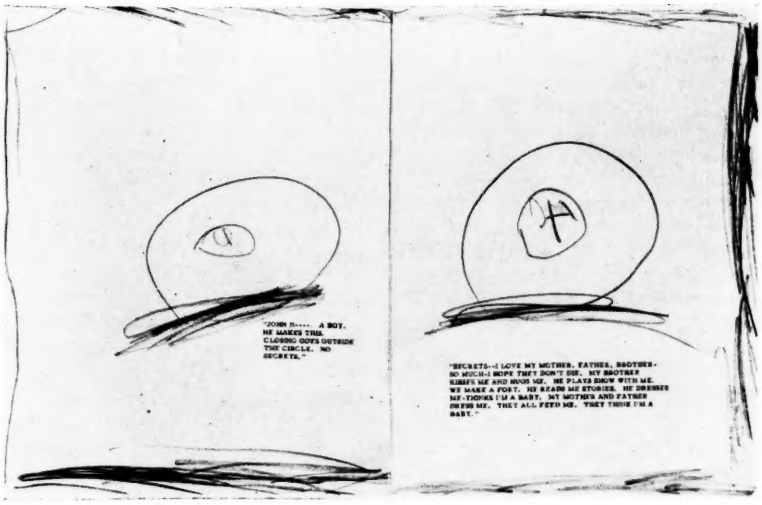
"JOHN N..... A BOY.
HE MAKES THIS.
CLOSING GOES OUTSIDE
THE CIRCLE. NO
SECRETS."
"SECRETS—I LOVE MY MOTHER, FATHER, BROTHER
SO MUCH—I HOPE THEY DON'T DIE. MY BROTHER
KISSES ME AND HUGS ME. HE PLAYS KNOW WITH ME.
WE MAKE A FORT. HE READS ME STORIES. HE DRESSES
ME—THINKS I'M A BABY. MY MOTHER AND FATHER
FEED ME. THEY ALL PETO ME. THEY THINK I'M A
BABY."

Fig. 2

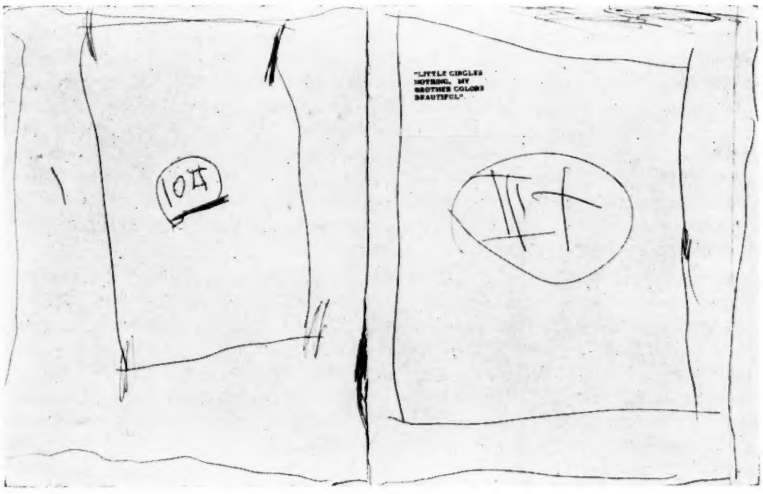

Fig. 3

In making the diagram on the left she said, "This is John N..... a boy. He makes this. (The closing goes outside the circle). *I have no secrets.*"

In the third interview, illustrated in Figure 3, there is further simplification, and Betty said, "The little circles are nothing. My brother colors beautiful." The drawings and the discussion contain much of psychodynamic import not pertinent to this paper.

On October 8, 1952, the mother reported that Betty had been moved to her

own bedroom, that she had stopped taking Phenergan and using the ointment. She stated, "The rash is 90 per cent better than when I first came here. Why is she better? Doctors have done a lot of harm to us." A week later she reported that the improvement in the skin had been maintained. At this point she began to reject her child openly by saying, "She was difficult from the day she was born. I love the child, but I don't do anything right with her. She drives me mad with her talking. She is always telling me something. We are entitled to our ways of doing things, but we have given all. I was overanxious and I still am, but I was never tense until the children were born. I expected them to grow up beautifully. *What's the point of all this talk?*" In two final visits, with Betty's skin still 90 per cent better, the mother again openly rejected her child and said, "*Why must I talk to you about my problems? It's Betty who's sick. Let her go to a psychiatrist when she grows up. It's her problem.*" She suddenly discontinued coming, without saying why, in October, 1952. During this last interview she made one important statement: "I am beginning to look at people with a different eye." She was asked to read *Emotional Problems of Living* by English and Pearson.

Nothing was learned of the progress of Betty's eczema until September 17, 1953, just one year after she was first seen. The mother reported over the telephone that the eczema had completely disappeared immediately after she stopped coming to see me, and that her skin had remained clear until August, 1953, when the eczema suddenly reappeared very severely only on the buttocks. She waited until February, 1954, before consulting me about the recurrence of the eczema, having consulted various dermatologists in the interim. Between February 4 and 12, 1954, there were three hourly visits with me, during which no progress was made, but finally the mother reluctantly disclosed the sequence of events which lead to the recurrence of the eczema. During the yearly checkup of the child by her pediatrician, the child was examined vaginally, and the pediatrician stated that her hymen was too fibrous and that she would have difficulty having sexual relations later on. He therefore put his finger in the vagina and ruptured the hymen. The child reacted with great anxiety and pain which lasted three days. Her buttocks broke out in full eczema within a week, and this gradually spread over the body and to the face. She then developed a series of behavior problems which included refusal to go on the toilet, demanding enemas, and refusal to urinate except into a bedpan.

When I saw Betty, she refused to discuss with me her attitude toward the doctor who had hurt her and refused to make any drawings. She said, "I don't tell secrets to anyone." During the time that the mother disclosed her own guilt in permitting the rupture of the hymen without considering the consequences, Betty's facial eczema started to clear up. The mother disclaimed any understanding of the relationship between the incident and the recurrence of the eczema. It is of significance that on one occasion Betty came to see me with a lock and key, and showed me how the key opened the lock, discussing the mechanism at length.

Psychotherapeutic interviews continued with the mother, who began to get some insight into the nature of the traumatic events which had occurred. One month later, on March 29, 1954, Betty's buttocks had cleared up completely, and she drew a picture of the doctor who had ruptured the hymen, and then tore it up in a rage, saying that it was a "scribble-scrabble of Dr. X." At the same time she drew the picture shown in Figure 4 and stated, "The doctor hurt me when I had my school checkup. I won't tell you. Let Mommie tell you. He stuck it all the way up—almost."

There was a slight increase in the eczema following this interview. Between March 29 and May 4, 1954, the mother and child were seen approximately every ten days, and during this time the general problems of the family were discussed.

Betty scratched occasionally, and announced that her mother didn't really love her. She began to withhold her bowel movements again, thus regressing to her earlier methods of dealing with her difficulties. In addition, she asked her mother to wipe her whenever she had a bowel movement. On April 27, 1954, the mother said that Betty and her brother "horsed around." "It's sexual play. It's repulsive.

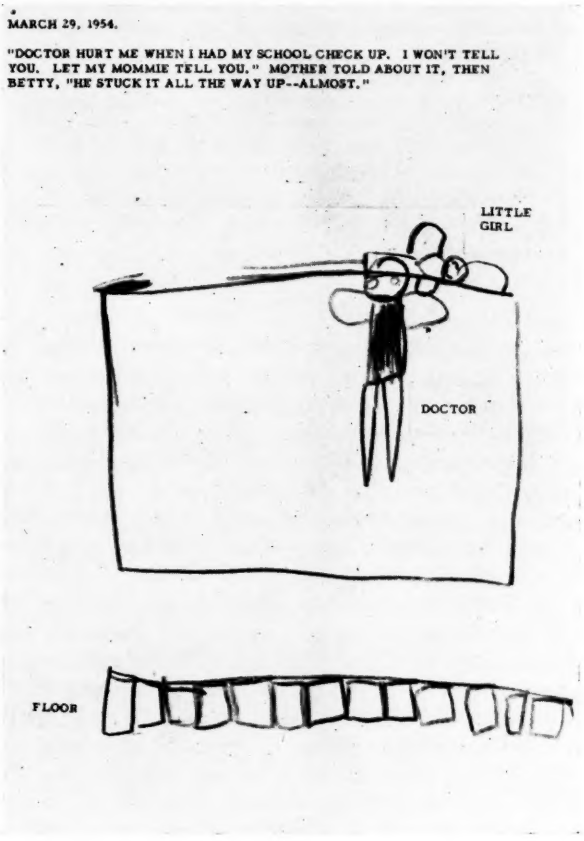
MARCH 29, 1954.
"DOCTOR HURT ME WHEN I HAD MY SCHOOL CHECK UP. I WON'T TELL YOU. LET MY MOMMIE TELL YOU." MOTHER TOLD ABOUT IT, THEN BETTY, "HE STUCK IT ALL THE WAY UP--ALMOST."
LITTLE GIRL
DOCTOR
FLOOR

Fig. 4

He plays in bed with her. He takes her around and kisses her. He lies on top of her and she on him. She insisted on seeing him in a jock strap." On May 4 it was reported that the child started to ask a good many questions about the doctors she had seen, reliving some of her earlier experiences and fears of doctors. On June 4 the mother said, "I could always make her see things my way. She's a passive child." The meaning of this attitude toward Betty was discussed in detail with the mother. On June 18 Betty's rash looked better, but she began to suck her thumb, and at this time her submissiveness toward her mother decreased. Her mother said, "She is getting hard to handle. She wants her own way. She

is fighting me. She says 'I hate you.' She used to be submissive and never leave my side. I could always make her see things my way. When she fights with her brother she goes wild. She says that she hates her grandmother, and she tells me what to do. She has stopped saying, 'You don't love me anymore.' "

The child was put on a course of cortisone at this time to eliminate the residual eczema. She was seen on June 29 at the end of a course of cortisone, during which improvement took place continuously as her ability to express hostility increased, and the mother, through psychotherapy, was able to deal more effectively with this hostility.

Betty was not seen between June 29, 1954 and March 8, 1955, when the mother reported that Betty's skin had been clear without cortisone by August 17, 1954 and had remained so up to the present (April, 1955). The behavior problem had also disappeared except for occasional long periods of activity in the bathroom. The mother said, "I think she enjoys herself when she has a big bowel movement. She has her own room and she doesn't scratch any more. When she is angry now she goes to her own room and closes the door. She wants to be the center of attention."

DISCUSSION

This case is remarkable from two points of view. First, Betty, age four, suffering from a severe type of eczema, acted out before the physician certain "secrets" that she had with her brother, with itching and a feeling of warmth covering the body when her difficulties with her brother were brought to light through discussion of her own drawings. This was coincident with the disappearance of the eczema. When the child again developed eczema following rupture of the hymen, her mother denied the existence of the psychologic factor. She did not come to see me until all other therapeutic efforts had failed and the force of circumstances led her to accept the inevitable conclusion, so distasteful to her, that psychologic factors were the basic problem, the solution of which resulted again in the cure of her child. Again, psychosomatic therapy, during which the child tore to pieces the drawing of the physician who perforated her hymen, led to recovery after several months, complicated by a regression to earlier methods of solving her guilty fears. All this took place during a period when the hostility of the mother to the child was only too evident. Although the mother openly rejected her child, the eczema disappeared when the child's anxieties were understood both by the child and me; the mother's hostility, nevertheless, was present and patent. This fits in to a certain extent with a previous paper on this subject, in which the theory of maternal rejection is considered in some detail and an alternate theory is proposed.[1]

I am reluctant to label this case as psychogenic eczema, because I believe that all illness is psychosomatic, with both mind and body components. I feel, however, that here the allergic components were negligible compared with the psychogenic forces. If we understand that psychogenic factors can no more act alone than can somatogenic forces, for practical purposes this is a case of essentially psychogenic eczema in childhood.

SUMMARY

A little girl, age seventeen months, refused to have bowel movements, this withholding sometimes lasting for periods of ten days. The pediatrician considered this "only a behavior problem," but after it had lasted for more than a year the family became actively concerned and insisted that x-ray studies be done. A tentative diagnosis of Hirschsprung's disease was proved to be false. At age three, after the diagnostic barium enemas, eczema began to appear on the buttocks, gradually spreading to the entire body.

The child was first seen by me at age four. On the basis of the drawings she made and of interviews with the child, it became apparent that a traumatic event had occurred connected with the brother when the bowel movements were first retained. The little girl acted out this psychologically traumatic event during therapy, and thereafter the eczema disappeared completely six weeks later.

About a year later, at age five, the child was examined by a pediatrician who found that her hymen was "fibrotic" and placed her on the examining table, inserted his finger in the vagina and ruptured the hymen. The child was very frightened, and shortly afterwards developed a rash on the buttocks, which spread gradually over the body and face. Over several months there was no response, either somatic or psychologic. Then, with the acting out of her hostility toward the pediatrician and the emergence of normal agression toward the mother, the eczema again disappeared. The mother was of the "rejecting" type, but the eczema disappeared nevertheless under therapy. The sequence of events in this case indicates that the eczema in this child is essentially psychogenic in origin.

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133 East 58th Street

Submitted April 28, 1955

The application of the principles of science to the diagnosis and treatment of disease is only one limited aspect of medical practice. The practice of medicine in its broadest sense includes the whole relationship of the physician with his patient. It is an art, based to an increasing extent on the medical sciences, but comprising much that still remains outside the realm of any science. The art of medicine and the science of medicine are not antagonistic but supplementary to each other. There is no more contradiction between the science of medicine and the art of medicine than between the science of aeronautics and the art of flying.—FRANCIS W. PEABODY (1881-1927)—*The Care of the Patient.*

TREATISE ON ASTHMA (MAGALA FI-L-RABU)

MAIMONIDES (RaMbaM)

(Historical Document)

CHAPTER II. MEDICAL TREATMENT OF THE ILLNESS

The ingredients of medicines to be given should function to clear the lungs and strengthen the brains (psyche), to return the organs of the body to a normal state, and to dry up all secretions, so that the disease should not spread.

From the experience of other physicians it has been known that the ingredients of medicines used for this illness should primarily work on the brains (psyche). When there is an open sore somewhere on the body doctors have known that pastes and lotions used locally would dry up the secretions and clear the wound. Do not use medicines that are too strong, they will not be good because they dull the brains (psyche). Medicines should be mixed in such a way that the power of their individual ingredients could be used to advantage. For clearing of phlegm from the lungs use expectorants only. Expectorants used should be strong enough to bring forth the phlegm without irritating the insides of the lungs. Galen was of the opinion that medications should not be too strong. The insides of the lungs should be kept moist so that the phlegm could be expectorated with ease. Some times it is hard to fall asleep because there is a feeling that secretions are dropping down and are irritating the lungs. On such occasions medication is necessary. To obtain the correct medical care one should be treated by a specialist. It is the duty of the specialist to be sure that the patient is being treated in a correct way. Sometimes one treats the patient from knowledge obtained by reading books only, and the patient becomes worse instead of better. Practical experience is often more important than theory, but it is best to combine both. Care should be taken when changing from one form of treatment to another, this should not be done too abruptly. The

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Maimonides (also known as Abû Imrâm Mûsâ ibn Maimûn, or RaMbaM, abbreviation for Rabbi Moses be Maimon) was born in Cordova, Spain, in 1135 and died in Cairo, Egypt, in 1204. He is widely known for his great works in theology, philosophy and astronomy. His reputation as a physician was so great that in 1171 he was appointed court physician to the Saladin. His "Treatise on Asthma" was written about 1190 at the request of the Saladin's Minister who had asthma. The treatise consists of thirteen chapters and an introduction and was originally written in Arabic (Mâgâla fi-l-rabu). It was translated into Latin (Tractatus contra passionem asthmaticum) by the noted French scholar Armengaud de Blaise at Montpelier in 1302. The Latin version was translated into Hebrew by the noted physician Rabbi Samuel ben Benvenishti the Saragossan in 1320. This translation was published by R. Mass, Jerusalem in 1940 with commentary and explanatory notes by S. Munter.

Thanks are due J. Mauer, R.N., New York City (formerly of Tel Aviv, Israel) for her kind assistance. Because of its medical and historic interest it is planned to translate the remainder of the treatise shortly.

physician, who the patient places his trust in, should possess theoretical and practical knowledge. Unless the physician is able to combine the theoretical and practical knowledge, he is like the sailor who lets his ship be led by the winds. Sometimes the winds blow the way he wishes but many times he is drowned needlessly. Many physicians practice in this way and like the sailor some patients escape and others die needlessly.

Abugrât as well as Galen stated that the practise of medicine is composed of a combination of theory and practise and the knowledge of the property of drugs. If it is important to purge the patient, this should be done. To bring forth the phlegm, expectorants and if necessary fumigants should be used. All these also tend to dry up the lung secretions and strengthen the brains (psyche). I am going to mention several types of medication which has proved to be of value and upon which one may rely. The body should be emptied by a mild laxative. It is good to purge the organism twice each year. If one is troubled by too much phlegm it is advisable to use a laxative in the spring. I am sure that if my advice is taken, it should be sufficient to purge oneself only once, and this in the spring. When a patient has an attack he should take only small amounts of food at each meal. He should dring sweetened drinks and chicken soup, all this helps to bring up the phlegm. If the patient also has accompanying chills barley water should be given. Generally nothing more will be necessary. However, if all this is of no help, then an enema will be necessary and this should be of the mildest type. If the enema does not clean out the organism and the patient does not feel too weak, then a laxative should be given, here also one should start with the mildest type. If all this does not accomplish the desired effect, expectorants or fumigants may be necessary to remove the secretions from the lungs which are in a congested state. If the secretions from the lungs are flowing freely do not use any medicines. If all this does not work, emetica should be used. This should be taken from time to time. Try to sleep very little and try to sleep in the daytime. On falling asleep do not permit yourself to fall into a deep sleep but rouse yourself soon after falling asleep, and sit in a chair. Try to sleep supported in a half sitting position. Drink very little water and then only when thirsty. Do not bathe or perform gymnastics. However, minor exercises performed with care, step by step are beneficial during the attack.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

HOW YOUR COLLEGE WORKS

Beginning with this issue the first of a series of essays entitled "How Your College Works" will be published in the ANNALS OF ALLERGY. These essays represent the answers to many hundreds of questions which have been sent in, over many years, to the home office—or most often posed at the annual meetings. Among others are:

"What is the editorial policy of the ANNALS?"

"What does such-and-such a Committee really do?"

"How does the Nominating Committee work?"

"To whom do I send suggestions for a change in the Instructional Course?"

"How are the dates and places of the Annual Meeting chosen?"

"What can I do for the College?"

"How are the College finances handled?"

These and other questions tell the officers that the Fellows take a lively and personal interest in College affairs. But for every determined question-asker, there must be others who are shy and diffident, or who are not certain as to whom to go.

Some of the answers, of course, are available in the constitution and by-laws. Some are carried in the minutes of the Board of Regents' sessions. In the past, some have been discussed at the annual business meetings. Some are part of the business of the various committees. Many others, however, are buried in the history, tradition and "lore" of the College. They represent patterns never actually formed in words and, therefore, never actually published in print. They are outward and visible signs of the inward, often unspoken, questions which influence every College member's activity. "Why *is* there an American College of Allergists? *What* is it trying to do?"

Any questions which you have, should be sent to any officer or committee chairman, who will see to it that it is directed properly for immediate reply by letter, or, if it is of sufficient general interest, for comment in these pages.

Progress in Allergy

HEADACHE

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HEADACHE is a symptom that few, if any, mortals have never experienced. A survey[1] of 4,634 individuals by the writer has shown that 3,005, or 64.8 per cent, have experienced recurrent headache of one type or another at some time in their lives. Affecting as many people as it does, in varying incidence, kind and degree, headache elicits universal interest both of patient and physician.

HISTORICAL BACKGROUND

One of the most intriguing types of headache is that which occurs in the presence of otherwise good health, and which is characterized by recurrence and a pulsating or throbbing type of head pain. According to Alvarez,[2] migraine was referred to as long ago as 3,000 B.C., in a Sumerian epic poem which contained the following verses:

"The sick-eyed says not 'I am sick-eyed.'
The sick-headed says not 'I am sick-headed.'"

In ancient Semitic poetry each statement used to be repeated twice in a slightly different wording. In our case, this means that the "sick-eyed," perhaps with a scintillating scotomata, was also "sick-headed." Alvarez therefore believes this to be the first written account of migraine.

Rothlin[3] states that in comparison the Greco-Roman writers, who are usually cited as giving the first description of migraine, may be considered nearly modern. Those most often quoted are Aretaeus of Cappadocia, who gave a fairly exact definition of classic migraine in the first century A.D., and Galen in the second century A.D., who gave the malady the name of hemicrania. The word is derived from *hemi* or half, and *Kranion* or skull. Through the years this word has been changed to *migraine*.

An excellent study of headache was made by Fothergill in 1778.[4] He recognized certain headache patterns, the relation of headache to various factors, and emphasized the importance and frequency of frontal headache, but his conclusions have not been well remembered. It is interesting to note how closely some of Fothergill's conclusions were later confirmed by the writer.[1]

During the nineteenth century it seems that attention became more or less focused on classic migraine. In an article "The Paroxysmal Neuroses

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(Nerve Storms),"[5] we find an excellent and thorough description of migraine. When we realize that this appeared in 1886, we must conclude that all of our progress has not been only in recent years.

The historic development of ergot therapy in migraine has recently been neatly summarized by Rothlin,[3] and we find that in 1883, Eulenburg[6] used injections of ergot extract in the "vasoparalytic form of hemicrania." In 1894, Thomson[7] advocated fluid extract of ergot by mouth as soon as the premonitory symptoms of migraine are noticed. He appears to have been the first to propose rectal administration of ergot to abort migraine. However, it was not until 1926 that the therapeutic application of ergot in migraine was established on a more solid basis. In that year, Maier[8] discussed the effectiveness of ergotamine tartrate in the treatment of migraine, and in 1928, Tzanck[9] published the first systematic study of twelve cases. Shortly thereafter, American workers, notably Lennox,[10] O'Sullivan,[11] Von Storch,[12] Alvarez[13] and others, were able to confirm the efficacy of ergotamine tartrate in the treatment of migraine.

Recent years have seen a great increase in investigative work on the causes and treatment of headache. In 1948 Wolff[14] published in his book the findings and conclusions of many careful studies. It will be impossible to review all of his findings in a discussion of this type; however, it should be pointed out that this work was a milestone in our progress.

THE PROBLEM OF HEADACHE

It has been said that the three most common complaints of mankind are colds, constipation and headaches. Since headache is such a common complaint and since it is so frequently seen in medical practice, there have been thousands of articles written on this subject. Unfortunately, in many of the articles there has been much "rehashing" or reduplication of material. Due to the great multiplicity of published articles, the reviewer has decided to try to present the topic as he sees it. A complete review of all published articles would be a virtual impossibility.

It should also be stated that the various publications relating to headache in general reflect the primary interest of the investigator. There are several divergent viewpoints regarding both the causes and treatment of headache. If the worker considers the problem from one particular approach, to the relative exclusion of others, a faulty perspective may be the end result. As an example, the allergist may think in terms of allergic causes of headache, the otolaryngologist may regard it as being due primarily to a nasal infection or abnormality, the ophthalmologist may regard it as being associated with an ocular disturbance, and the psychiatrist or psychoanalyst may think primarily of his approach. The obvious conclusion is that basically we need an *overall* approach to the whole problem. In this discussion we will therefore attempt to evaluate the various approaches to headache.

Headache is a common, even everyday, problem in the practice of an

allergist. The essential point to us is being able to recognize the relative importance of allergic factors. As will be pointed out later, vascular headache may be precipitated or "triggered" by a number of causes. Often, several of these causes may be of importance in the same individual. Anyone interested in the proper management of headache must take every facet of the problem into consideration. Even among allergists there is some difference of opinion. There are some who feel that allergy to foods is the main cause of allergic headache, while others, including myself, feel that inhalant sensitizations are of paramount importance.

Years ago in my office practice I was impressed by the fact that headache so often accompanied nasal allergy, even though in some cases the nasal involvement was only minor in degree. At the Southern Medical Association meeting in 1947, I reported cases of headache that were clearly due to sensitization to house dust.[15] All this led to my realization that this aspect of the headache problem required further study and emphasis.

First, let us recognize that there are two varieties of headache, the vascular and the nonvascular. Obviously, certain organic conditions are included in the latter category. For this reason a careful differential diagnosis is essential. As an example, we cannot neglect an old depressed skull fracture, intracranial neoplasia, subdural hemorrhage, aneurysms, et cetera. Therefore, our diagnostic approach must be careful and thorough. X-ray, electroencephalography, ophthalmoscopic examinations, and other tests may be required.

In this discussion, however, we are primarily interested in the vascular type of headache and, then, in the importance of allergy. In order properly to evaluate the headache problem, we must first consider the causes and mechanisms of headache. Wolff[14] lists the following pain-sensitive structures in the head:

1. Tissues covering the cranium, especially arterial.
2. Intracranial structures.
   (a) Parts of dura mater
   (b) Dural arteries
   (c) Venous sinuses
   (d) Cerebral arteries at base
3. Cranial nerves V, IX and X.
4. Cervical nerves I, II and III.

From the clinical standpoint, the following sources of pain are of special importance: (1) Nasal and paranasal structures, (2) intracranial vessels, (3) extracranial vessels, and (4) muscles of head and neck.

Before discussing the mechanisms of headache, there are a few important points relative to vascular headache which should be stated.

Aural or prodromal signs are seen in the stage of constriction. These aurae may include visual changes, scintillating scotomata, mood changes, vertigo, and paresthesias. Then there is an increased amplitude of pulsation in the stage of dilation. The pain is often throbbing in character. Nausea and even vomiting are frequent. Visual changes may also persist. Later, the vessel walls become edematous and rigid, and therefore more refractory to vasoconstrictors. At times, the person may have many of the symptoms of vascular headache, but the pains may appear in unusual locations such as the face, shoulders, or chest. These pains have been called "migraine variants." Also, the person may at times have many of the symptoms of vascular headache or even of classic migraine, but there is no pain. Recognition of this may explain certain symptoms that may appear at intervals, such as nausea and vomiting or transitory difficulties in vision. This has been called a "migraine equivalent." Myalgia, which is associated with tension of the scalp or neck muscles often accompanies or follows vascular headache. The person with headache involuntarily tends to splint these muscles and this results in pain. This factor may be of distinct importance in frequently recurring headaches.

Many workers regard the response of the vessel wall to a specific vasoconstrictor, such as an ergotamine, as being a diagnostic point in vascular headache. We see that when a drug of this type is given *early*, the headache attack may be aborted or terminated.

In a recent publication Wolff[17] has discussed the mechanisms of headache in considerable detail. While a good deal of factual data is reported, it is possible for the reviewer to mention only some of the more important and salient findings. One of these findings was that pain accompanying distention of the ventricle is due to traction resulting from displacement of the large arteries in the circle of Willis. Wolff also points out that traction and displacement of pain-sensitive structures, rather than pressure changes *per se,* are responsible for headache associated with brain tumor.

He also has shown that stress or emotional conflicts may produce nasal changes which may result in headache. He feels that pain from the nose arises principally from the nasal "approaches," such as the turbinates and nasofrontal ducts. However, the reviewer feels that headache arising from nasal structures has a different mechanism; but the reviewer and Wolff are in agreement in that inflammation in the sinuses themselves has been found to be a rare cause of headache.

In discussing the intravenous injection of histamine, Wolff[17] said that during the injection there was a maximum histamine content in the blood stream, a falling blood pressure, but no headache. During the period of infusion there was not much change in the amplitude of intra- or extracranial pulsations. When the infusion was stopped, however, the blood pressure returned to its normal level and exceeded it for a brief moment.

There was a coincident rise in the amplitude of the pulsations and the headache began. Thus, the amplitude of pulsations increased and pain began with diminishing concentration of circulating histamine, and when the blood pressure had returned to normal.

Wolff[17] also quoted Loveless in the incidence of headache after "overdosage" in pollen-sensitive individuals. This also may lead to the conclusion that nasal reactions may result in headache.

Also, Wolff,[17] in a discussion of his work and that of Ostfeld,[124] stated:

"It is postulated that small as well as large vessels participate in the headache experience by altering hydrostatic pressure in the capillaries, so that water and all lower molecular weight substances leak into the surrounding tissue juice in greater than normal amount. Among these lower molecular weight substances are agents which have the capacity to lower pain thresholds and damage tissue.

"Vasoconstrictor agents, by altering the capillary hydrostatic pressure so as to draw fluid and pain-threshold lowering substances back into plasma, reduce local edema, raise pain threshold, and diminish the intensity of headache concomitantly."

Ostfeld and his co-workers[18] showed that about half of the patients experienced weight gain of from two to seventeen pounds usually preceding headache, followed by diuresis with weight loss during the phase of dwindling intensity of the headache. There was commonly retention of sodium, potassium, and corticosteroids, as well as of water, before headache, with outpouring of these substances during the diuresis. Also Ostfeld showed that diuresis during a period of weight gain may not affect the ensuing headache, and that weight gain provoked in migraine patients by hormonal means does not necessarily result in headache. Therefore it was concluded that headache and overhydration are concomitant phenomena which are not causally related.

Tunis and Wolff[19] reached the conclusion that there is not only an amplitude change relevant to migraine headache, but that edema of the vessel wall makes change in the state of contraction of the artery more likely to induce headache.

Wolff[17] calls attention to the fact that in the tissue fluids in headache there may be an agent or agents capable of lowering pain thresholds.

STATISTICAL SURVEY

There has been much work on the pathologic physiology of headache and on groups of headache sufferers, but I felt that a large scale study of the general population would give us certain information.[1] This information could not be obtained merely by study of a group of patients who had headache of such severity as to warrant treatment by a physician. It was felt that all background factors must be adequately studied. Mild or only occasional headaches should also be discussed.

It has not been generally recognized that many physicians have had to rely on headache statistics that are based on either small studies, or

on groups of patients. Studies on small groups are not statistically significant. Studies on patients provide figures which are true for sick people only, and cannot be interpreted as being true for the general population. A worker may quote a certain figure which is requoted again and again, and finally becomes an "established fact;" however, the statistical reliability of the original figures was insufficient to warrant their conclusions.

In a pilot study involving 251 office patients with respiratory allergy, I found that 58 per cent had sufficient frontal headaches to warrant complaint and discussion, whereas in a control group of 100 young adult individuals with no symptoms, the incidence of frontal headache was only 27 per cent. Anyone with nasal symptoms or frequent colds was excluded from the control group.

This problem obviously warranted further study. Sandoz Pharmaceuticals furnished a grant to the Louisiana State University School of Medicine which made it possible to begin planning this study early in 1949.

It was recognized that sampling the population at random would not give accurate figures; therefore, throughout the survey 95 per cent cooperation of any group surveyed was deemed essential. This would give a cross section view of the group. Several groups that did not cooperate to this extent were discarded and the data not used. Nearly 6000 individuals were included in the gross sample, but only 4,634 satisfactorily cooperating individuals in groups were reported.

In order to cross check accuracy, three separate surveying procedures were employed. We designated these groups as follows: Group I, the general group, consisted of heterogeneous individuals, who were employes of Charity, Southern Baptist, and Eye, Ear, Nose, and Throat Hospitals in New Orleans. Obviously this group included various types of personnel and almost paralleled the general adult employed population. Here the questionnaires were distributed and collected through the direct help of management.

Then, in order to determine whether there would be any great difference between answers of this type and those obtained by interviewers, it was arranged to interview personally several diverse categories of individuals. This part of the survey was designated as Group II. These individuals were homogeneous in their various classes, and included salesmen, saleswomen, housewives, white manual laborers, and Negro manual laborers.

Group III consisted of five separate classes of individuals whose intelligence was of high enough level so that accurate responses could be anticipated without interviewing. This included freshmen medical students, senior medical students, physicians, and White and Negro Catholic Sisters.

Group IV was simply the total of these previously mentioned groups.

It was seen that comparable findings in different groups adequately

paralleled each other in almost all instances. This fact indicates that each of the methods of study provided reliable data.

Questionnaire findings were transposed to IBM cards. After this was done, calculations and computations could be made on virtually any combination or relationship desired. Incidentally, the data which were reported represent only a part of the virtually infinite number of relationships which it is possible to obtain.

It is not the purpose of this review to go into the findings of this survey in any detail since they have already been reported in the literature.[1,20,21,23] However, it is pertinent to this review to summarize some of the findings, particularly since they indicate the relationship of the allergic state to headache.

The data obtained gave us some idea of the frequency of the various types of vascular headache. We were somewhat surprised that the incidence of "classic" migraine was found to be lower than was anticipated. Among those with headache, 13.2 per cent had migraine when it was rather broadly defined. When the definition was made more strict, it was found that this syndrome was present in only 5.2 per cent of those with headache. It should be pointed out, however, that we felt that pain in the temporal regions was more diagnostic of migraine than was pain in other areas. Others may have a different view.

Of those with headache, 29.8 per cent complained of a throbbing type of pain. In 15.6 per cent, the pain was present in the occipital area.

There has been a great deal of discussion of histamine cephalalgia in the literature. When this syndrome was rigidly defined, we found it to be a clinical rarity. Here again, we must remember that the incidence of a headache pattern depends on the particular definition of the investigator. Some workers report a much higher incidence, obviously due to the fact that they regard many cases of frontal headache as being histamine cephalalgia.

By far the most common type of headache is that found in the frontal area, which includes not only the forehead, bridge of the nose, and eyes, but also the upper part of the face. This type was found in 72.7 per cent of all persons with headache.

We also found that the incidence of headache is greater among females, younger adults, single people, educated individuals, students and professional groups. At this point it may be of interest to list certain data (See table).

Some of these data were tested by Dr. Huldah Bancroft, Professor of Biostatistics at Tulane University and were found to be statistically significant. These findings make it obvious that there is a connection between the presence of nasal symptoms and the incidence of headache. It may be concluded that many of these nasal disturbances are allergic in nature. There also seems to be a relationship between headache and other manifestations of clinical allergy. Also, there is a higher familial history

PER CENT INCIDENCE OF RESPIRATORY OR ALLERGIC DISEASES AND RELATED DATA

	No Headache	All Types Headache	Frontal Headache	Migraine Headache
Hay fever	6.8	10.4	10.4	12.9
Running nose	3.8	7.8	8.1	9.7
Sneezing spells	5.7	13.5	13.5	18.1
Itching nose, eyes	4.1	11.9	12.1	18.7
Discharge from nose	3.0	5.7	5.9	11.6
Discharge from eyes	2.0	3.7	3.8	10.3
Blocked nose	3.8	13.3	14.0	23.2
Drip back of throat	5.0	17.8	19.3	27.1
Sinus trouble	3.6	14.9	15.7	29.0
Not troubled with any of the above	81.2	55.1	53.3	35.5
Asthma or wheezing	2.6	3.5	3.3	5.8
Repeated coughs	2.4	5.4	5.6	7.1
Frequent sore throats	2.3	9.8	10.0	17.4
Phlegm in throat	4.7	15.2	15.8	27.7
Have none of above	86.4	72.1	71.1	53.6
No colds	23.4	7.8	7.1	4.5
One or two per year	64.6	70.2	69.6	74.8
Three to six per year	6.7	17.9	19.2	18.1
Almost constantly	1.0	3.3	3.3	1.9
Constantly	0.4	0.8	0.8	0.6
Use nose drops usually	2.0	6.3	6.5	9.7
Use nose drops during colds	20.5	41.3	43.0	49.7
Never use drops	74.1	52.4	50.5	40.6
Have hives	3.7	7.1	7.6	14.2
Have eczema	1.0	2.4	2.3	5.2
Have Poison Ivy	2.8	5.0	5.1	3.9
None of above	88.2	86.5	86.1	78.7
Allergy in family	11.3	25.1	26.5	39.4
None	86.0	74.9	73.5	60.6

of allergy among those with headache as contrasted to those with no headache.

Since these figures were based on a cross section survey of 4,634 individuals, it appears to the writer that there is a definite relationship from the statistical standpoint between allergy and headache. While other workers may postulate that allergic manifestations may be primarily psychogenic in origin, it must be conceded that the majority of these complaints are based on an antigen-antibody mechanism. Such allergic reactions do not necessarily have to be due to sensitization to foods, inhalants, molds, et cetera, but may also be associated with bacterial infection or allergy.

As stated above, these data also showed that frontal headache is the most common or everyday type of headache.[21] It is also felt that the diagnosis of histamine cephalalgia has been used too indiscriminately. Histamine cephalalgia is a specific severe unilateral type of headache, which is of short duration, and is accompanied by lacrimation, nasal blockage, and flushing on the affected side. Usually the attacks last for less than an hour, and often awaken the patient at night. The visual disturbances, nausea and vomiting, which are typical of migraine, do not occur in this condition, and there is an absence of the strong hereditary tendency. It differs from trigeminal neuralgia in the fact that trigger zones are absent, and because the pain does not follow the distribution

of the fifth nerve. An important diagnostic point is that the subcutaneous injection of histamine base may precipitate a typical attack in from several minutes to an hour. This response must be distinguished from the relatively immediate generalized headache that may follow histamine injection, which is often a more general reaction in the intracranial vessels. Therefore, the immediate appearance of pain after histamine does not necessarily indicate histamine cephalalgia; however, others feel that this type of pain appears promptly. Freedom from attacks is said to be obtained by using histamine in therapy, with the idea of increasing the vascular tolerance, or by producing a so-called "refractory state" to histamine. In this condition, as in migraine, the pain may be reduced in intensity by sitting up or by standing.

FRONTAL HEADACHE

Since frontal headache appears to be a specific syndrome, it should be described.[21] It was observed that many of the patients stated that frontal headaches appeared or were worse during the times that nasal symptoms were more prominent. The use of vasoconstrictors in the nose gave relief to some.

On the other hand, headache might be present when nasal symptoms were minimal or even absent at the time of onset of the headache. Some patients stated that relief often occurred when nasal discharge became more abundant. It was seen that at times there was only minor correlation between the amount or degree of nasal blockage or other nasal symptoms and the onset of head pain. Therefore, we could not state that the headache depended on the *degree* of local nasal reaction.

In the extrinsic or noninfective type of nasal allergy, headache could often be precipitated by an overdosage of the antigen. While the head pain could appear in a few minutes after injection, in some patients its onset would be delayed for several hours. In this delayed type of reaction the time interval was fairly constant. Local reactions at the site of injections were usually quite moderate, even though subsequent headache appeared. There was a universal trend to improvement in the headaches which coincided with improvement of the nasal condition during hyposensitization.

It was found that frontal headache had a variable period of duration, lasting from a half hour to several days and even weeks. Nausea and even vomiting appeared during the headache in a large number of patients. Prodromal aurae were not consistently observed, although vertigo and visual changes, including scotomata, were occasionally present during attacks. In a small number of patients, fever appeared during the headache.

Characteristically, the frontal pains were bilateral, and were localized in the region of the forehead. In many patients the pains were unilateral at times; unilateral and bilateral pains may alternate. Occasionally, dis-

comfort is also felt in the region of the eyes, across the bridge of the nose or even into the face. In a few patients the pain later radiated to the vertex or to the temporal regions, or even over the entire head. In many patients, pain was also present in the occipital region. As stated above, pains in the posterior neck muscles may accompany or follow pain in any part of the head.

It was found that the frontal type of headache possesses at times some of the characteristics of migraine, or the symptomatology that has become identified with vascular headaches. These include prodromal symptoms such as aurae, visual difficulties, nausea and even vomiting, throbbing type of headache, et cetera. Also, in a recent study[20] I found that the ergotamine drugs are effective in an impressive percentage of cases of frontal headache. The ergotamine drugs are known to be exceptionally helpful as vasoconstrictors of cranial vessels. While some may feel that the response seen in individuals with frontal headache is due to nasal decongestion, the author feels that it is due to the direct constricting effect of the ergotamines on arterial musculature.

The anterior and posterior ethmoidal arteries are branches of the ophthalmic, which also gives off anterior meningeal and frontal branches. It is apparent that edema of the nasal mucosa would produce some degree of pressure even though minor on the vessel walls, and thereby possibly initiate vasodilation in the anterior meningeal branch of the ophthalmic or in other branches. Thereby frontal pain could be produced. The nasal pressure would act as the "trigger." The supraorbital artery (and frontal branch) is a terminal branch of the ophthalmic artery. In some cases of frontal headache this artery is palpable and visibly dilated. It is also recognized that the ophthalmic arteries are branches of the internal carotid vessels. It has been thought by many that the effect of the ergotamines is principally on the branches of the external carotid. However, we cannot say that the ergotamines do not constrict the branches of the internal carotid, since there is no definite anatomic, physiologic, or clinical proof of this idea.

I have found that the antihistamines frequently relieve frontal headache. This may be due to the effect on the nasal mucosa. Also, vasoconstrictors used properly in the nose may relieve pain, and I instruct my patients in the technique of the lateral head low position. It must be remembered, however, that nasal medications of this type may be distinctly habit forming. The phenomenon of rebound turgescence is now well appreciated.[24] In some cases, relief has been obtained after the use of vasoconstrictor solutions in the nose has been discontinued.

Since nasal symptoms seem to be associated so definitely with frontal headache, it seems to be hardly necessary to point out that the management of these cases should include a diagnostic allergy survey. The recognition and proper treatment of the respiratory allergy will often give good results. The writer has personally seen many cases of frontal headache

who have been helped by the proper management of their nasal allergy. However, there are many investigators who do not feel that allergy is an important cause of headache.

ALLERGY AND HEADACHE

Critchley and Ferguson[25] wrote that "Migraine has been the happy hunting ground of the theorist, and the problem has been attacked by representatives of all branches of medicine. Each in turn has discovered in migraine phenomena pertaining to his own specialty." Schwartz[26] adds "Not the least the allergists have participated in these attacks, and from many textbooks on allergy, one derives the impression that they captured the prey."

Schwartz[26] interviewed 3,815 relatives of 191 asthmatic and 200 normal nonallergic persons, and fifty patients with baker's asthma. He found an identical incidence of migraine in the relatives of asthmatic patients as compared to nonallergic persons. He therefore felt that migraine has no hereditary relationship with asthma. He also found that of 171 patients with migraine none gave a history of probable allergic factors eliciting their headaches. Skin tests and circulating eosinophils did not differ from values obtained on normal, nonallergic persons. He therefore concluded that migraine is probably only rarely of allergic nature.

To the reviewer, the use of the word "relatives" is somewhat confusing. Since he states that they were *interviewed*, it is possible that these included *cousins*, as well as close blood relatives, but all living. This point is not clear to me. In our questionnaire the term *"blood relative"* was used. This was explained to participating groups and persons as including parents, grandparents, uncles, aunts, brothers and sisters. We were interested in determining the incidence of clinical allergy in the families of those with headache. As stated above, we found a much higher familial history of allergy in those with headache as contrasted to those without headache. Also, in our work, we did not limit the studies only to persons with migraine, since all types of headache were included.

Schwartz also was unable to correlate allergic factors with headaches. He states that "It must be admitted that this questioning does not by itself exclude the possibility of allergy to food as being involved in the mechanism of migraine, but it is surprising that not even a suggestion of such mechanism was found. Studies of food by the elimination of one item or the other were not made, as most of the patients were seen only once or twice." It is the opinion of the reviewer that the latter part of the preceding statement is of importance and significance. Each case of headache requires careful individualized study in order properly to evaluate all possible causative factors.

Many other investigators have taught in the past that the factor of allergy in headache is of comparatively little importance. However, today this tendency is becoming less pronounced. As an example, until recently, psychiatrists and neurologists have to a great extent discounted the im-

portance of allergy. Many of them believe that the allergic reaction is predicated largely on a psychogenic mechanism. It is somewhat of a surprise to find that certain of these are now discussing allergic causes of headache. The reviewer feels that as we acquire more knowledge concerning headache mechanisms we are carried to the inescapable conclusion that there are several basic mechanisms which may play an active part in the causation of headache. In one individual, personality problems may be the trigger mechanism of headache on many occasions, but at certain times attacks may be brought on by an allergic reaction or by any of the causes which will be enumerated later.

Over a period of five years Kallós and Kallós-Deffner[106] studied 184 patients with migraine and found twenty-eight of them to have both migraine and asthma, hay fever and/or angioedema. It was found that exposure to the specific allergen, whether by injection, inhalation, or ingestion, always produced a typical migrainous attack concomitant with asthma, hay fever and/or angioedema. They conclude that the migrainous attacks in these cases and under the conditions mentioned were produced by an allergic mechanism.

The concept of allergy as a factor in headache is not new. Trousseau[27] in 1873 observed that migraine is frequently found in persons suffering with asthma. Brown[28] in 1921, and later Vaughan[29] in 1927, discussed the fact that allergy may be a factor. LaRoche, Richet, and St. Girons[30] in 1930 also called attention to the importance of allergy. Other authors including Goltman,[31,32] Balyeat and Rinkel,[33] Eyermann,[34] Coca, Walzer, and Thommen,[35] Randolph,[36] Feinberg[37] and others have also discussed allergic factors in headache. Also in very recent years there have been other workers who have recognized and amplified these concepts. However for a period of several years the literature was relatively barren from the standpoint of discussion of allergic causes of headache.

In 1952, Unger and Unger[38] in a study of fifty-five patients concluded that 80 per cent were either completely or almost completely relieved of attacks by the detection and elimination of causative foods. They felt that migraine is basically an allergic disease, and that allergy to foods is the prime precipitating cause of attacks. They also graphically pointed out the fact that on one occasion the factor of stress may produce migraine, while on another occasion an allergic reaction may have this effect in the same individual.

Albert Unger in another report[39] points out that many patients have headaches which are clearly associated with nasal symptoms, but he also states that similiar headaches may occur in the absence of nasal symptoms. He agrees with the reviewer that there has been too much emphasis placed on defining headache syndromes. He quotes Hilger[40]: "The subject must be taught and dealt with as a vascular imbalance with its expression a vasodilating pain and its locale limited only by the anatomic location of the peripheral branches of the carotid artery. The fog of

typical and atypical migraines, histamine cephalalgias, pseudosinus headache, and atypical neuralgias is thus swept aside, and the simple mind can go forward to meet disturbed vascular physiology in whatever locale it may be found."

Unger[39] again emphasizes the findings of Unger and Unger[38] that foods are the main precipitating cause of most attacks of migraine. He states that the specific foods are determined by the use of elimination diets, feeding tests, and food diaries. The most troublesome foods are milk, chocolate, wheat, and pork.

The reviewer is completely in accord with the statement that milk allergy is the most important food sensitization to be considered; however, he feels that chocolate has been somewhat overrated. Many patients state that they think that chocolate has caused headache—after drinking a chocolate flavored milk drink. The real reason may have been due to the overindulgence in milk. Sensitization to commonly eaten foods often appears only after a large amount of the particular food has been ingested. The patient may be able to tolerate small or minimal amounts of the food without the appearance of headache.

Alvarez[41] feels that headaches thought to be allergic in nature may have a psychosomatic basis.

Zanfagna[42] concurs that allergy as a basic causative factor must be considered in cases of frontal headache associated with nasal symptoms.

Therefore, the reviewer sums up all this information with the following statements: Frontal headache is often due specifically to sensitization to an inhalant antigen, such as house dust. Other types of vascular headache, especially classic migraine, may be due to allergy to foods and also may be due to sensitization to an inhalant substance. However, the important point to be emphasized is that all types of vascular headaches may be due to an allergic type of reaction.

STRESS

The factor of stress as a cause of headache is most important. I think that we all agree that vascular headache is often closely tied in with psychologic, emotional or personality problems. This may be important to a greater or lesser degree in almost all cases. We must remember that the changes in the vessel walls which appear during headache may be initiated or "triggered" by many causes. Also we recognize that stress is constantly or almost constantly present in many persons.

Friedman[43] states "It has been postulated that exposure to noxious stimuli both physiologic and psychologic, of sufficient or prolonged intensity, results in the inability of the body to adapt to stress which in turn causes certain vasomotor changes in the cranial circulation, eventually producing cranial pain. The mechanism by which the nervous and hormonal systems function in producing these physiologic changes is but partially understood."

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Friedman, von Storch and Merritt[44] found that they were not able to relate migraine to a dysfunction of the pituitary-adrenal system. However, they added that the sensitivity and validity of these tests are yet to be substantiated. In the same publication they state that the personality make-up of patients with migraine is extremely variable and may be influenced by a variety of emotional factors. This means that there is little evidence of specificity of precipitating psychodynamic factors. They also state that an understanding of the underlying psychologic factors plays an important part in the management of migraine.

They postulate that patients with migraine react poorly to stress for two reasons. One is the factor of heredity; the mechanism through which this operates has not been clearly elucidated, but it is possibly related to an imbalance of the autonomic nervous system. The second reason is based on the fact that they have an insecure personality pattern which interferes with their adjustment to their environment.

According to Wolff[45] threats are defined as environmental stimuli that evoke reactions of an adaptive or protective nature, commonly with accompanying feelings of being unsure, uncertain, or in danger; but such reactions may be evoked in the absence of these feelings. Threats may be of different types, and may affect an individual in different ways. As an example, circumstances that jeopardize our position in life may be regarded as a threat, and threats may have various end results. As another example, severe nasal reactions may accompany anger, embarrassment, et cetera. Your reviewer has already emphasized the relationship between nasal reactions and headache. Wolff also points out that changes in vascular function, as in headache, may be the result of sustained adaptive reactions. He also states that patients with headache exhibit greater variability in the contractile state of certain portions of the vascular tree, even during headache free phases.

Wolff also found that ophthalmic slit lamp examination of vessels in the bulbar conjunctiva shows dilatation of the arterioles and venules during headache and that tissues may become more pain sensitive during headache, due to a lowering of the pain threshold. Hematomas may also occur. He postulates that increased capillary permeability may result from arteriolar dilatation and slowed blood flow, which allows fluid and pain threshold substances in the plasma to enter the tissues.

The expression "tension headache" has been used rather loosely. To some workers this indicates the type of headache which appears after an episode of stress or emotional tension. To other workers, "tension headache" is primarily muscle pain or myalgia which results from headache.

In an article by the reviewer[46] the following statements are made:

"Let us discuss the personality changes that are generally accepted as being characteristic of migraine or in fact of many other headaches. It is my observation

that headache patients may be difficult to handle; at times unpleasant, and possibly unco-operative, demanding and aggressive. They are often impatient and intolerant of anything except immediate results. This personality pattern is generally tied in with the migrainous individual as a cause of his condition. Therefore, the thought is herewith advanced that the personality changes may at times be secondary to the headache state—rather than a cause. The patient who obtains relief may become more pleasant and less 'tense.'

"The physician who is interested in headache often sees many individuals who have just about exhausted the possibilities of aid that may be given to them by various medical specialties.

"Another point to consider is the fact that at times the headache patient may obtain dramatic relief from some spectacular procedure. As an example, refraction and the wearing of glasses may relieve headache for a period of time, possibly weeks or months. Then the headaches return in their former intensity. There are several medical procedures which may be regarded by the layman as being spectacular or dramatic. An allergy survey, a psychiatric study, psychoanalysis, teeth extraction, gynecologic surgery, sinus operation, other nasal surgery, et cetera, may fall into this category."

Also in my book[17] the following comments are included:

"There has been a growing belief in recent years that all or most vascular headaches are due to emotional factors or to a state of tension. This fairly widespread belief may have hindered other approaches to the headache problem or to other types of studies. Our work has certainly confirmed the importance of tension—but only to a certain point.

Also many people recognize the existence of a special variety of headache, which they call 'tension headache.' In this condition the aches and pains are thought to follow a definite pattern. However, I feel that we have no more right to talk about 'tension headache' as a special variety than we do about smokers' headaches, menstrual headaches, weekend headaches, etc. The reason for this belief is that we should not label a certain type of headache just by naming the cause; on the other hand, since headaches of all types are so frequently brought on by tension we can't just limit its importance to one particular type of headache. The term "tension headache" is therefore thought to be too general, and will probably disappear when the different varieties of headache are better defined, or if we stop trying to classify various types of headaches and just regard them all as being vascular headaches.

"The power of suggestion is a wonderful thing. In my years of practice I have heard of people getting relief from all sorts of unusual sources—including enemas, various and sundry operations on other areas of the body, faith healing, et cetera. I am surprised that I haven't heard of relief of headaches among those religious cultists who handle live rattlesnakes."

It is therefore obvious that emotional and stress factors are of definite importance in headache. These factors may be of greater or lesser importance. Anyone who has practiced medicine for a number of years will conclude that most of us have personality difficulties of one type or another. These difficulties or personality problems may be associated with our work, personal factors and general makeup. Feelings of hostility may be a factor and at times the hostility may not be recognized by the patient. I recall the case of a doctor's secretary who was clearly allergic to milk. Drinking excessive quantities of milk would cause head-

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ache. However, her attacks would occur mainly during certain months of the year. I finally found out that this period was during the months that her mother would visit her. My patient was married, with her own home, husband and children. Although she loved her mother, unrecognized feelings of hostility would develop during the visit—because during this time my patient was more or less put into the background. The mother made all decisions regarding meals, entertainment, et cetera, and my patient felt as though she were "playing second fiddle." The proper recognition of this situation was essential in order to handle her case properly. However, she also was clearly allergic to milk. The emotional reaction would trigger the attack. At other times of the year she might be better able to tolerate the drinking of milk.

In this particular case, it might have been easy to lay the blame entirely on emotions, without a recognition of the allergic factor. I have repeatedly emphasized the importance of emotions and tension in headache; however, I, as well as others, would be wrong to stress the importance of emotions so strongly that other possible causes would be overlooked. This has happened all too frequently.

Anyone interested in headache must be at least an amateur psychiatrist and try to evaluate the problems which bother our patients. At times this is relatively easy to do, but in difficult cases it may be better to consult a psychiatrist.

The important point to remember is that we must take all facets of the problem into consideration. Overemphasis on only one of these facets may result in imperfect therapeutic results. To this reviewer the factors of emotional tension or stress, and the factor of allergy are both of paramount importance. Unfortunately, the latter aspect has been occasionally somewhat neglected.

One of the reasons for the lack of emphasis on allergic diseases was very well stated by Dr. J. Harvey Black, whom I quote:[48]

> "The young doctor who is just beginning his practice is usually quite surprised to learn that conditions which he seldom saw and treated lightly in the hospital now are rather plentiful and require more help than he may be prepared to give. Unfortunately for the teaching of young men, the common allergic conditions do not often require hospitalization. For this reason, the teachers of medicine themselves are not fully aware of the frequency and the importance of the conditions in private practice, and teaching suffers on that account."

Another proof of the importance and prevalence of allergic disorders is furnished by the fact that there are now a tremendous number of medicinal preparations available which have been developed to alleviate or help these various troubles.

Moench[49] made the interesting observation that headache is a common complaint in psychoneurotic patients, but is rare in psychotic patients.

OTHER FACTORS OR CAUSES TO BE CONSIDERED

Ophthalmologists have found that many of their patients complain of headache, which is usually found to be associated with an error of refraction or with muscle imbalance. Renken[50] states that there are two types of imbalance: In the "tropias" there is an obvious lack of co-ordination of the ocular muscles, in the "phorias" the imbalance is not superficially evident, since the muscles seem to work well and in proper balance; however, the constant strain to keep the eyes parallel may result in headache. In this latter group, the imbalance may be corrected by prisms, exercise or by operation.

Errors of refraction may also be associated with headache. Lanchner[51] in a large scale study found that astigmatism was the main finding, followed by presbyopia, and then hypermetropia. There was only one case of high myopia. He also found that frontal headache was the most common type of headache in those with ocular findings.

Wolff[14] offers an explanation why some patients suffer with headaches and why others with the same ocular defect do not. He believes that in addition to an error of refraction or muscle imbalance there is a state of emotional tension, so that there is a cumulative effect of the two factors, either one of which in itself could cause headache.

Ophthalmologists state that it has been concluded that headache which ordinarily appears in the morning is not due to an ocular disturbance. This type of headache usually appears during the day, although exceptions to this rule may be found in glaucoma or in uveitis.

In ophthalmoplegic migraine there is an associated disturbance of ocular muscle action. Patrikios[52] feels that pyretotherapy is helpful in this condition. Bramwell[53] has suggested that aneurysms may produce ophthalmoplegic migraine, but other workers have suggested that edema involving the central nervous system may be responsible.

Partial or total loss of vision may accompany migraine according to Walsh.[54] He also describes other abnormal visual sensations, visual imagery, and diplopia, and made the interesting statement that swelling of the eyelids may accompany headache. The reviewer also has found that edema of the lids may at times be present during attacks of frontal headache, which may be additional proof of the fact that there is an underlying vascular disorder.

This returns us again to the question of the mechanism of frontal headache. For many years this type of pain has been ascribed to "sinusitis." Most otorhinolaryngologists feel that headache may be seen in acute sinus infections but only rarely in the chronic type. Patients with frontal headache have a recurring type of headache, which may "come and go." It is also generally believed that the so-called "vacuum" type of headache is not the cause of these pains. The author also does not agree with the belief that frontal headache arises necessarily *per se* from painful irritation of the turbinates or vasofrontal ducts. Headache arising

from various nasal structures has been shown to be referred to different parts of the head and face[14] and not specifically to the frontal region. For the reasons previously stated it is felt by the author that frontal headache is essentially due to a vascular disturbance involving branches or the main vessel of the ophthalmic artery.

However, pain may arise from involvement of nasal structures. Lischkoff[55] states that anatomic anomalies causing head pain may include: (1) Deviated septum, (2) impaction of middle turbinate, (3) a bulging ethmoid cell or bulla ethmoidalis.

Headache may result from acute infectious coryza or from an allergic reaction in the nose, according to O'Neil, Morrison, Green, Kovar and Wigton.[56] Symptomatic relief may be obtained by shrinkage of the edematous nasal mucosa.

Anderson and Rubin[57] point out that secondary vasodilating pain arising from the nose or paranasal sinuses follows a definite sequence. First there is an aching pain, which changes to a throbbing type of pain during the stage of vasodilation; then when edema of the vessel walls has occurred, the pain again becomes aching in nature. They conclude that the nose plays a greater part in headache production than is generally realized.

Neuralgias of nasal origin may produce headache according to Boies.[58] Various types of facial neuralgias may be present; however, in the opinion of the reviewer, neuralgias may be distinguished from vascular headache, since they are usually sharp and lancinating in character.

Anderson[59] also stated that the use of a local anesthetic, such as cocaine, in the nose may indicate whether or not pain specifically arises from an involved area in the nasal mucosa. It is obvious that nasal surgery is indicated at times in certain selected patients, but it is also recognized that many nasal abnormalities are essentially allergic in nature.

In many cases, it is necessary to secure a consultation with a neurosurgeon. Various types of organic pathology must be ruled out at times before the diagnosis of vascular headache is correct or tenable. Even when this is correctly done, as physicians we must recognize our limitations in the matter of diagnosis. A young girl once consulted me because of headache. I was suspicious of brain tumor, but neurologic studies and electroencephalogram were all negative. I was unable to help her, and later at operation she was found to have an inoperable cerebral malignancy. Whenever there is a question of organic pathology, all diagnostic measures must be utilized.

Disorders involving the cervical vertebrae as a cause of headache have been discussed. Braaf and Rosner[60] stated that chronic headache may be treated effectively by head traction. Cervical myelography, cervical laminectomy and removal of a damaged disc were also recommended to be done when indicated. They also stated that exercise of the muscles of the back of the neck may be beneficial.

Raney and Raney[61] discussed headache in association with herniated

cervical discs. They found that digital pressure in the occiput could produce radiating pain to the temporal, orbital and facial regions. They also stated that head pain due to a pathologic cervical disc is not relieved by section of the root of the trigeminal nerve nor by tractotomy nor by both, even when the pain is confined within the zone made anesthetic or analgesic.

Later Skillern[62] stated that pain may arise by way of the descending or sensory root of the trigeminal nerve, as a reflex pain having its origin through C 2 and C 3 level from a painful greater occipital nerve.

Then Judovich and Nobel[63] stated "The facts which seem to be in agreement are: (1) that occipital pain, headache, and facial pain may exist alone or in conjunction with signs which involve the cervical spine; (2) that a tender point in the occiput is frequently found, and that stimulating this area may cause local pain or produce radiating pain to the temple, orbit, or face; and (3) that local anesthesia of this tender occipital point may abolish the headache." The same authors state that headache in these patients is vascular in origin. Cervical pain may be a "trigger mechanism."

They found that an acutely tender point is usually found in the occiput, approximately midway between the tip of the mastoid and the midcervical spine. The tender area may be present on both sides if bilateral headache is present. They state that "Both the occipital nerve and artery are located at this tender point. Radiation to the temple, orbit, and face is far beyond the distribution of the occipital nerve, and since the occipital trigeminal reflex appears to be untenable, arterial pain remains as another possibility. When we consider that the superficial temporal artery and carotid artery are simultaneously tender with the occiput, and that injecting the occiptal tender point with an anesthetic can abolish the temporal, orbital, and facial pain, then we may reasonably consider a vascular basis for this pain."

Two per cent procaine is infiltrated into the tender area which has been shaved. When pain subsides after the infiltration, it does so immediately.

They also state that patients with headache should have the cervical spine routinely examined to eliminate this structure as an etiologic factor. Headache may be relieved by head traction using thirty-five to forty pound weights. In addition to this, they obtained symptomatic relief in patients whose headache is associated with painful lesions of the cervical spine by the use of Hydergine,® a vasodilator. This fact and the response to a local anesthetic, to the authors indicates a vasoconstrictive mechanism. They conclude that cervical and scalp muscle spasm does not appear to play an important role in this type of headache or in tension headache.

Vasodilators have been used in the treatment of headache and will be discussed later. At this point, it is well to emphasize that hypertensive headache is of the vascular type. Friedman[64] states that in headaches associated with hypertension, increased blood pressure is not commensurate

with the degree of headache. It is recognized that pain may occur when the blood pressure is high or low. If the contractile state of the arteries is impaired, headache may result.[14]

Hypertensive headaches are usually not accompanied by the usual symptoms of vascular headache, such as scotomatas, nausea and vomiting. Schumacher and Wolff[65] expressed the opinion that headaches associated with hypertension, as well as those associated with migraine, were essentially produced by the same mechanism.

In recent years new drugs have been added to our armamentarium which are very effective in the treatment of hypertension, and have aided us in the management of this type of headache.

While it is not the purpose of this review to discuss various points in the differential diagnosis of headache, it is becoming more and more obvious that this question is of interest to workers in various medical specialties. The treatment of hypertension, as an example, properly belongs in the realm of the internist or general practitioner, as do other medical conditions complicated by headache. Morgan[66] also points out that headache is often associated with gastrointestinal disturbances, and may be seen with systemic diseases, toxemias without fever associated with diseases of the liver and kidney, and in other conditions.

Gynecologists have long been interested in headache. Headache is often associated with the common condition of premenstrual tension. During this period, when there may be a marked change in both emotional and physical states, vascular headache is very likely to occur. Many women state that headache only appears at this time. Premenstrual tension should be regarded as a "trigger mechanism."

Methyl testosterone has been used in the treatment of migraine in women. Moehlig[67] reports its use in sixty patients and observed that forty-nine were improved, adding that treatment must be carefully supervised because undesirable secondary effects are likely to result. Hirsutism appeared in twelve, acne in twenty-seven, deepening of voice in thirteen, menstrual disturbances in twenty-nine, increase in weight in forty, nervousness in eighteen, and increase in libido in twenty-eight. It is the opinion of the reviewer that the likelihood of these side effects, and possibly others, greatly outweighs any advantages which might be gained by its use. There are other methods of treatment which will give beneficial results and which do not carry these risks. However, it should be stated that small doses of methyl testosterone (with constant supervision) will decrease the incidence of masculinization.

Some gynecologists have taught for years that organic changes in the pelvic organs may result in headache; therefore much surgery has been performed with this end at least partially in mind. Undoubtedly, many a uterus has been vainly sacrificed in the hope of relieving vascular headache.

There is also an obstetric aspect to the problem. Allergists are aware of

the fact that in many women allergic disorders improve during pregnancy, but also that in many others these conditions may become more severe. Since we feel that many headaches have an allergic basis, we would expect this tendency to reflect itself during pregnancy. This does happen in many women, who will state that their headaches are worse during pregnancy. Other workers may postulate that this increase in some patients may result from hormonal changes, or from the emotional and stress factors which may be prominent during pregnancy.

According to Derbes and Engelhardt,[68] the effect of pregnancy on asthma varies from complete relief from attacks during this period to extreme exacerbation of symptoms.

Also in some women, headaches may become almost continuous. Fuerstenberg[69] has suggested the term "status cephalalgia" for continuous headache. This term does not connote the same limitations as does the term "status migrainous" which has been used by many authors.

Pediatricians are aware of the frequency of headache in childhood. Krupp and Friedman[70] studied 100 children with headache. Of seventy-five with migraine 35 per cent complained of headaches before the fourth year. They found no difference between the two sexes, and that abdominal complaints were prominent. Balyeat and Rinkel[71] state that in children prodromal symptoms are languor, loss of appetite, and abdominal discomfort. Fever frequently occurs, and acute infection may be suspected.

Glaser[72] states that migraine occurs in children of all ages from infancy onward, that it may be allergic in origin, and due to sensitization to foods. He found the most common offenders to be chocolate, egg, wheat, and milk. Inhalant sensitizations may also be a factor according to Stoesser.[73] He also found that antihistamines may be helpful.

The reviewer[1] found an incidence of headache of 78.7 per cent in young adults up to the age of twenty, in marked contrast to the figure of 28.6 per cent for those over sixty.

One may ask why headache decreases with advancing years. Is it due to a lessening of causative factors, or is it due to a lessening of vascular lability dependent on gradual, even though mild, sclerosis of the vessel walls? One may ask, is it due to a lower incidence of extrinsic allergy, or is it due to the fact that the older person is more stable, less volatile, and less influenced by his surroundings? It is obvious that older people in general do not have as many tensions (due to sex, ambition, economic status, et cetera) as do younger persons. It is also possible that there may be in general a lesser amount of clinical allergy in older persons. Many of us have observed in our practice that we see proportionately more children and young adults than we do older persons. This statement takes into consideration the fact that there are more younger people than there are older ones.

The factor of sex tension as a precipitating cause must not be over-

looked. We found a greater incidence of headache among single or divorced persons as compared to married ones.[1] It is easy to conclude that marital stability is an important factor, not only in headache, but in other and varied conditions. Statistics have definitely shown that married persons live longer than do single ones. Also, illicit relationships do not furnish the basic tranquilizing effect of marriage.

While most headaches are of the vascular type, many diagnostic problems may arise during study of the patient. There are pathologic states which may mimic this condition. The aid of a neurologist or neurosurgeon is often essential, in order to be absolutely sure that a patient does not have one of the other varied types of headache. At times the proper treatment of the individual with headache must be surgical in nature. It is impossible to discuss this question in detail in this presentation. Post-traumatic headaches, brain tumors, depressed skull fractures, and subdural hematomas, are only a few of the many conditions that at times must be considered.

In the differential diagnosis of headache, electroencephalography may be helpful at times, even though it is not generally conceded that there is a wave pattern characteristic of headache. However, this procedure may at times help to rule out organic changes.[74] There has been some discussion regarding a possible connection between headache and epilepsy, but this connection is generally conceded to be obscure.

The relationship between migraine and the convulsive states was studied by Friedman and Cohn,[75] who concluded that almost half the cases of true migraine show significant electroencephalographic changes, and that cases which show particularly slow wave activity respond well to anticonvulsant medication. Weil[76] stated that an electroencephalographically recognized type of migraine was seen in eight subjects. Anticonvulsant medications were helpful in these patients, and he suggested the term "dysrhythmic migraine."

A statistical analysis[144] which showed an 8 per cent incidence of migraine, as against a 0.5 per cent incidence for epilepsy, led to the conclusion that among 2,500 people one case of migraine combined with epilepsy occurred.

In a later report, Weil[77] stated that forty-two migraine patients were studied clinically, pharmacologically and by EEG. Ten subjects (24 per cent) showed abnormal to grossly abnormal electroencephalograms, as well as neurologic-psychiatric findings and pharmacologic responses usually not observed in "ordinary" migraine. To him this justifies the term "dysrhythmic migraine."

It may be interesting here to mention the observations of Lippman,[78] who has found that hallucinations, or a sense of distortion of the body image, may occur in association with migraine. In his report he discusses seven such cases.

CAUSES OF VASCULAR HEADACHE

At this point let us discuss some of the causes of vascular headache. The following data[79] are divided into three groups. The first or "trigger" factors lists some of the immediate precipitating causes of headache. In the second group predisposing situations, conditions or states are mentioned. Then in the third group, factors which are both trigger and predisposing are listed. A discussion of this type calls to mind the number of mechanisms which may be associated with vascular headache. It is hardly necessary to elaborate on these factors in detail; however, it should be pointed out that each of them may be somewhat complex, and an individual discussion of each would be extremely time consuming. As an example, the taking of alcoholic drinks may produce headache in several ways:

1. The immediate vasodilating effect of alcohol may quickly precipitate an attack.
2. The hangover type headache also may be associated with dilation or increased amplitude of pulsation.[64]
3. Headache may be due to sensitization to the beverage itself. Many individuals cannot drink a certain beverage, such as beer, without developing headache.
4. Emotional factors may result from overindulgence.
5. Excessive smoking (associated with drinking) may produce nasal irritation.

"Trigger" or precipitating causes include nonspecific factors (temperature changes, hunger, fatigue, et cetera), allergic reactions, excessive smoking, alcoholic drinks, emotional episodes, toxic states, and vasodilator substances. Predisposing factors are mechanical lesions of the cervical spine, unmarried state, occupation, hypertension, nasal allergy or abnormality, sex, heredity, age and advanced education. Some factors are both trigger and predisposing, such as sex tension, endocrine, nasal, stress, eye, age, biochemical factors, mental conditioning, et cetera.

The threshold required to produce headache varies from patient to patient. In other words, the addition of various factors required to produce headache may be greater in one individual than in another.

It therefore is obvious that it is necessary to evaluate properly all possible causative factors in the study of the individual with headache. If our approach is oriented exclusively in one direction, therapeutic results may be inadequate and unsatisfactory.

Before treatment is instituted, our diagnostic study must be thorough and complete. We must first of all be certain that vascular headache is present. The patient may present symptoms of more than one type of headache. Often patients will state that they have two or even three separate and recognizable varieties of headache. As an example, a person who has frontal headache in conjunction with nasal symptoms may also

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at times have symptoms suggestive of involvement of other vessels, such as generalized headache which may be due to dilation of intracranial vessels. On still another occasion symptoms of "classic" migraine may be present. The important point is to recognize that vascular headache is clearly present. We must also remember that the attack may be complicated by muscle spasm, increased emotional tension, and other features of vascular headache.

While it is not the purpose of this review to discuss the *differential diagnosis* of all types of headache, it must be emphasized that specific problems often arise, as, for example, differentiating temporal arteritis. Excellent descriptions of these matters will be found in books by Wolff,[14] Friedman,[64] Ryan,[80] Moench,[49] and others.

Blumenthal and Fuchs[81] give an excellent description of temporal arteritis. "This is an extremely rare condition observed exclusively in older age groups in which headache is one manifestation of an obvious systemic disorder. The associated symptoms include fever, weakness, anorexia, weight loss, anemia and leukocytosis. Diagnosis is based on the presence of painful tender nodules of the scalp along the course of temporal arteries. There is a high incidence of retinal artery involvement with partial to complete blindness. The treatment consists of resection of the segment of the involved artery. Recent reports of response to adrenal steroids are difficult to confirm because of the small number of patients."

Fleming and Grossman[82] state that there is a predominance in females, and that the onset may be insidious or sudden. The pathologic picture is one of panarteritis with necrosis of the media and formation of granulomatous tissue containing foreign body giant cells and epithelioid cells. The intima becomes thickened and thrombosis is sometimes present. The presence of eosinophils has been described in a few cases. They state that "it runs a course similar to that of a chronic infectious or, in some cases, a hypersensitivity (collagen) disease." They also state that they have seen cases in younger age groups that resembled temporal arteritis, were afebrile, and in whom microscopic examination of the vessel walls did not reveal abnormalities.

Nadler[83] reports similar cases in a group of patients between twenty-five and forty-five years of age, who were temporarily relieved by digital pressure over the involved artery and periarterial infiltration of one per cent procaine. There was no fever, and microscopic examination was negative.

Patzer, Derbes and Engelhardt[146] have shown that migraine may be helped by the periarterial infiltration of eucupine and procaine hydrochloride.

Fleming and Grossman[82] state that infiltration with 1 per cent procaine is a valuable therapeutic aid in treating certain headaches, regardless of their etiology. They state that surgical excision of involved extracranial arteries may be indicated in some cases of temporal arteritis. However,

the reviewer feels that this condition (temporal arteritis) is relatively uncommon and is only rarely seen in practice, while, on the other hand, other varieties of vascular headache are frequently seen. The fact that eosinophils are present may add support to the thought that it may be associated with a hypersensitivity mechanism.

While discussing surgery of other types we may also quote Hilsinger,[84] "Unfortunate also, was the fact that the induced trauma from intranasal surgery gave temporary relief and led the surgeon to believe that this was the proper procedure; however, the relief in many cases was only transient."

Hilger[85-88] says that the cause of headache is vasospasm at the arteriolar level, caused by some poorly integrated autonomic stimulus. He also believes that all vascular headaches are fundamentally the same, the only difference being in the initiating cause, in location and in degree of vascular imbalance.

Hilsinger[84] goes on to say, "If the involved arterioles are terminal, they erect an effective dam, causing proximal, passive vasodilation due to the increased amount of blood pounding up against the constricting arteriole. If the arterioles are located within the walls of the parent artery, in the vaso-vasorum, the ischemia and resultant transudate cause a flaccidity of the muscular coat, with resultant vasodilatation. Either of these causes of vasodilatation stretches the periarterial sensory nerve plexus with resultant pain." He also states that the final accepted theory of the mechanism of pain may include a combination of factors—fatigue plus allergy, autonomic imbalance plus bodily depletion, et cetera.

Tunis and Wolff[19] observed that there is relative vasoconstriction, even during headache-free intervals, among headache subjects. They concluded that "Neither short-lived temporal artery constriction alone, nor brief contraction of temporal muscle alone, resulted in headache. When long sustained, muscle contraction alone or cranial artery constriction, *per se*, sometimes resulted in disagreeable head sensations or pain. The concurrence of the two more commonly resulted in headache. Indeed, sustained contraction of skeletal muscle and constriction of its nutrient artery were often concurrent in certain subjects and resulted in muscle contraction headache. This correlation was noted in normotensive as well as in hypertensive subjects."

Judovich et al[89] and Judovich[90] made some extremely interesting observations. Some of these were:

1. Cervical and scalp muscle spasm *per se* do not produce headache.

2. The actual factor which triggers pain mechanism is unknown, but is supposedly due to release of stress substances controlled by the hypothalamus.

3. It is noted that structures about the head and neck are more frequently involved in stress or emotional reactions than other areas.

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4. Certain muscles of the head and neck and their innervating structures are derived from the branchomeres, or gill system, so that autonomic efferent impulses regulate their muscles as well as somatic fibers. These muscles are regarded as branchial muscles. As such, they would be more likely to respond to stress and emotional states via the autonomic fibers than would purely somatic innervated muscles.

5. In short, it is postulated that the physical aspects of tension headache and the tension state may be regarded as a viscerosomatic reaction of the branchial innervated structures (innervated by fifth, seventh, ninth, tenth, and eleventh cranial nerves).

Further studies by Judovich and his associates[91] on spinal and postconcussion headaches show their results with hydrogenated ergotoxine alkaloids (Hydergine®) in sublingual doses of 1.5 to 3.0 mg, or dihydroergocristine (Malcodyn®) 1.5 to 3.0 mg. The special types of headache studied were those due to spinal puncture, myelogram, pneumoencephalogram, ventriculogram, combined pneumoencephalogram and ventriculogram, and post concussion headache. Placebo reactors were excluded. It was found that in seventy-three patients, who did not respond to analgesics or placebos, approximately 50 per cent obtained rapid relief of headache with hydrogenated ergotoxine alkaloids, suggesting that vasoconstriction is associated with the pain mechanism in a significant proportion of cases. Additional actions of these drugs have been reported, such as anti-stress properties and central sedative effect. What role these additional factors play in the relief of pain is undetermined at this time.

Tunis and Wolff[92] have called attention to the value of making analyses of cranial pulse waves. They state that "The pain of vascular headache results from increased tension within or about pain-sensitive cranial artery walls. Fundamental to the mechanism of headache of the migraine type is dilatation and distention of cranial arteries with resultive increase in such tension. However, intramural and perimural edema of the distended arteries summates in its effect with that of dilatation to intensify noxious stimulation and the severity of the headache."

It is becoming more apparent that an increased amplitude of pulsation, or a dilatation of the vessels may not be the major cause of pain in many cases of headache. The factor of edema of the vessel walls must definitely be considered. Delicate measurements of the size of an arterial vessel may reveal this increased size or increased amplitude of pulsation; however, this increased size may also be due to the presence of edema in the vessel walls. Therefore, the increased size or caliber of the vessel itself may be due to either of two factors. Also, as Judovich et al. have shown, the importance of vasoconstriction as a factor may have been neglected. All workers do, however, agree that there are arterial changes which are associated with vascular headache. As we progress, the exact pathologic physiology becomes clearer. The riddle of today becomes the fact of tomorrow.

Histamine is a product of the amino acid histidine, which is present in all complete protein. Thus, the probable precursor of histamine is found in all normal tissue, and histamine itself has been demonstrated in many body tissues.[145]

Histamine is a recognized vasodilator with which we are all familiar. Horton[93] has used it specifically in the treatment of histamine cephalalgia. Blue[94] also calls attention to the fact that it may be given by iontophoresis. The reviewer feels that the importance of histamine in the treatment of headache still has to be proven statistically. The injection of histamine may produce a generalized type of headache, very quickly, which may last for only a few minutes. In histamine cephalalgia, a typical attack may occur after a longer interval (within an hour) after it has been given. It must be remembered that the use of histamine is usually a dramatic type of treatment. Taking all this into consideration, the reviewer has not been inclined to use histamine routinely in treatment of headache. However, it is recommended at times that the injection of histamine subcutaneously be given as a diagnostic measure.

The use of nitroglycerin to induce attacks of migraine was proposed by Schnitker and Schnitker.[95] A modification of this technique has been employed by Dalsgaard-Nielsen[96] wherein he applies a 2 per cent nitroglycerin ointment to the forehead and temporal region. The standard dose is 6 mg of nitroglycerin. The headache, which develops in less than fifteen minutes, is elicited in 90 to 100 per cent of migraine patients and is said to be identical with their usual headache in 95 to 100 per cent. The test is discontinued by removal of the ointment, and the headache is relieved with an ergotamine preparation. As a matter of fact, the response of the patient to the injection of an ergotamine preparation is also an excellent diagnostic test.

Provocative tests of this type have a definite place in diagnosis. A positive reaction lends more support to the diagnosis of the vascular type of headache, and Dalsgaard-Nielsen[96] attributes great importance to the low headache threshold in the development of headache. Nicotinic acid has also been used as a provocative test.

One drug can have different effects on different sections of the vascular system according to Pichler,[97] after a study of the behavior of the cranial arteries of both cattle and of men. Four separate types of structure were distinguished.

Bovet and Gatti[98] feel that the possibility of an edema mechanism in headache and the evidence of a sensitive mechanism in the intracranial venous sinuses both emphasize the possible importance of the observed variations in cerebral venous pressure. They conclude, "Thus contrary to the classical views that the venous pressure mainly follows the general pattern of the arterial pressure, it was noted by blood pressure measurements in the external jugular vein of the dog that an independent venous hypotension (after adrenaline and ergotamine) and hypotension (nitrite

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derivatives, histamine) occurred which may be interpreted as being due to an active vasomotor control in the cerebral circulation."

SYMPTOMATIC TREATMENT OF VASCULAR HEADACHE

There have been many medications proposed for the relief of attacks of headache. As would be expected, patients vary in their response to these various medications, and such treatments must be individualized for each particular person. The medication used also depends on the type of headache that is present. As an example the treatment of frontal headache differs to some extent from the treatment of "classical migraine."

Antihistamines.—In many types of vascular headache (especially in the frontal variety), nasal reactions may be of definite importance. The mechanism of this type of headache[21] has been described and it has been stated that antihistamines may be of value. If the mechanism is primarily one of nasal mucosal edema, it is obvious that such therapy may be of considerable help and it has been found to be of special benefit during the early stage of treatment, immediately after hyposensitization has been started. If allergic edema of the nose is benefited, headache should also be helped. The use of antihistamines may also give relief in other types of vascular headache, particularly when the patient has knowingly or unknowingly been exposed to an antigen to which he is allergic. It should also be pointed out that the response to antihistamine medication is often "tailor-made;" in other words, optimum benefits with no side reactions may result from the use of one, but not from another.

Dramamine,® which is related to the antihistamines, has also been used in the treatment of headache. Vaisberg[100] reports dramatic and gratifying relief after the intravenous injection of this drug. He states that in each attack of migraine there was complete subsidence of the nausea with total relief of the pain within a matter of four minutes. The dose varied from 50 to 100 mg. In no instance did he find a therapeutic failure with the use of this preparation, and there were no undesirable side effects.

Vasoconstrictor Nose Drops.—Many patients are helped by the use of vasoconstrictor nose drops when used in the lateral head low position. Drops seem to be as effective as nasal sprays. Benefit after the use of nose drops may be hoped for in those patients who have nasal symptoms associated with attacks of headache; however, certain patients of this type are not relieved at all. McComiskey[24] and others have called attention to the fact that the indiscriminate use of vasoconstrictor solutions topically in the nose has been injudicious in many cases. The phenomenon of rebound turgescence has already been mentioned in this discussion. We frequently see individuals who are actually addicted to the use of these preparations, whether in the form of a spray, drops, or even an inhaler, and who have used these preparations several times a day over a period of years. The bald fact is that in many patients the symptoms are actually perpetuated by the use of these preparations, and these persons will often

be helped immediately if they can be persuaded to discontinue the habit. When told to stop, the patient will invariably throw up his or her hands and say "—but Doctor, I can't breathe or live without my nose drops!"

It has been the policy of the reviewer to postpone insisting upon the discontinuance of the habit until after the allergy survey has been completed, and after the patient is under treatment. It is then suggested that the patient leave the city for the week-end, while the nose drops remain in the medicine cabinet at home. During this time an antihistamine is given by mouth, and a sedative may be properly prescribed. At the end of a two- or three-day period of strict avoidance, the patient will usually report that the nasal symptoms have been greatly helped. Since headache is so often associated with nasal symptoms, knowledge of these facts will often be of great assistance to the physician in the proper management of stubborn cases of headache. On the other hand, it is often necessary to use vasoconstrictor preparations temporarily during an acute infection. Rarely they may also be used (again temporarily) in an individual who has seasonal hay fever of short duration.

Corticosteroids.—The response of the patients with typical migraine to the corticosteroids has not been spectacular. In view of the recognized possibility of undesired side effects due to their use, the reviewer does not suggest their use in headache of this type. On the other hand, prednisone or prednisolone may be tried by mouth in certain patients whose headaches are clearly associated with nasal symptoms, and who may be having a troublesome flareup of symptoms. The use of the hormones should be temporary and they should not be employed routinely.

In addition to the systemic use of hormone therapy, there has been considerable interest in topical use in the nose. In a recent placebo controlled study, Anderson and Ogden[101] found that the topical use of prednisolone was effective in thirty patients who had clearcut nasal allergy. In this work the initial tissue saturation method was employed, the preparation being used more frequently during the first forty-eight hours. No undesirable side effects were observed. Therefore, it is possible that there may be a place for a preparation of this type in the treatment of headache associated with nasal allergy.

Analgesics.—In the author's statistical studies[1] it was found that 82 per cent of people with headaches do not consult a physician, and that 81 per cent preferred aspirin or aspirin-containing compounds for relief. This figure of 82 per cent is possibly due to the general attitude on the part of many laymen that little if anything can be done to help them, an attitude resulting at least partially from the approach of the medical profession as a whole to the problem of headache. Unfortunately, there are many patients who have gone from physician to physician, or from specialist to specialist, in the vain hope that some therapeutic approach will relieve their sometimes severe and incapacitating headaches. Also, the figure

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of 82 per cent who do not seek medical aid may be due partly to the fact that many persons have only mild or occasional headaches. In this latter group that we find patients who are quite responsive, often to simple non-narcotic analgesics. It is also true that many persons are unaware of the fact that quite efficient medicinal preparations are available, with which they are completely unfamiliar.

Analgesic medications act by raising the pain threshold, and not by specific action on the involved vessels, such as occurs when vasoconstrictors are used. It must also be remembered that different persons have different pain thresholds, and some are more likely to be relieved by simpler medications.

It is the opinion of the writer that any and all narcotics are contraindicated in vascular headache,[20] because most of these headaches are chronic and recurrent, and addiction is always a possibility. Codeine is no exception to this statement, since many headache sufferers learn to rely heavily on this narcotic, which is definitely habit forming; many physicians, however, feel that it is safe to use codeine.

An effective combination (Fiorinal®) has been widely used, consisting of analgesics (acetylsalicylic acid, 200 mg, acetophenetidin 130 mg, a sedative (Sandoptal,® 50 mg), and caffeine 40 mg. We can readily see that such a combination is of help in the management of headache associated with emotional tension and muscle spasm. Numerous articles[44,102,103,105] have appeared reporting experiences with this preparation. It has also been recommended for pain due to sinusitis, otitis media, and other conditions and may be given more freely than certain other medications.

Hormones.—The use of the corticosteroids has already been mentioned, but other hormone therapy may also be indicated in carefully selected cases. The writer has already mentioned that the use of methyltestosterone in female patients carries with it the possible risks of undesirable side reactions; however, we must remember that endocrine disturbances may be important background factors. Estrogens may be useful in rare instances in menopausal patients. In individuals with hypothyroidism, the use of thyroid extract has been advocated by several authors.

Histamine.—A great deal has been written pro and con on the use of histamine. It has been used with varying degrees of results in different allergic disorders, according to numerous authors. It has been stated that the use of histamine may induce a refractory state in which the individual does not respond with clinical symptoms to the endogenous overproduction of this substance. We are all aware of the fact that this chemical is elaborated by the body cells as part of an allergic reaction. The use of the antihistamines is but one indication of the importance of this substance in allergic states. One concept is that histamine is produced in excess by cells which have been injured by the antigen-antibody reaction. We are all familiar with the fact that the administration of a large

amount of histamine base may produce flushing and headache, both of which effects are due to vasodilatation. Also dermographia of the skin is thought to be due to the production of an excessive amount of histamine.

Horton[106] reports benefits after its use in specific types of headache, and has described the syndrome of histamine cephalalgia which is also known as Horton's syndrome. While the reviewer's statistical findings[22] indicate that this syndrome is not common among the general population, it must be remembered that Horton in his experience at the Mayo Clinic has undoubtedly seen many cases which would not be met in the usual practice of medicine. It, therefore, follows that he is better qualified to properly appraise this method of treatment.

Blue[94] has suggested the administration of histamine by iontophoresis, and concludes that this type of therapy is beneficial in various allergic disorders including migraine. He states that the use of this method is simple, that less time is involved in its administration, and that the production of deposits in the skin caused a more persistent flush following its use.

Jonez[107,108] discussed repository injections of histamine, and found it to be effective. Histamine conjugates and histamine azoprotein are not widely used.

Intravenous injections are not usually suitable for routine office treatment, and the reviewer has always felt that they should be avoided whenever possible. He also feels that more statistical proof is necessary before we conclude that histamine therapy should be widely used in the treatment of headache.

Miscellaneous Methods of Treatment.—There are numerous other medications or methods of therapy which have been used in the treatment of headache. Some have a variable effect; for example, the use of oxygen has helped some individuals, but symptomatic relief is not found in enough individuals to warrant its routine use.

Diuretics seem to fall in the same category, as do treatments with various vitamins such as B_{12}.

The Use of Mood Changing Drugs.—Friedman[109] evaluated the use of Reserpine® in headache in 150 patients and concluded that "Patients with hypertension showed considerable improvement; those with tension headache, moderate improvement; and those with migraine, no definite relief." On the other hand, Barrett and Hansel[110] state that Reserpine in optimum doses is of definite value as a therapeutic adjunct, especially in the treatment of the resistant patterns as represented by the tension and migraine types. They add that it is also effective in the so-called histamine cephalalgia type, which they feel represents the majority of all types of vascular headaches.

Reserpine has been extensively used in emotional or mental difficulties and has been found to be quite effective, which would indicate that it

relieves the mental tension which may precipitate attacks of headache. It is a central depressant of the sympathetic nervous system; however, it has the objectionable feature of stimulating the nasal secretions and causing blockage in some individuals. Since nasal symptoms are so often associated with headache, this factor may be a definite hindrance to the use of this drug.

Reserpine belongs to the group of drugs known as "ataraxics." There are two broad divisions of this group, the first being represented by chlorpromazine (Thorazine®) which is also used in suppository form and the rauwolfia alkaloids, which are characterized by effects on the autonomic nervous system; the second type is represented by Meprobamate (Equanil® and Miltown®) which acts on the central nervous system only, without affecting autonomic functions. According to Berger[111] Meprobamate has three pharmacologic properties of unusual interest; they are muscle-relaxant action, anticonvulsant action, and a taming effect best observed in monkeys. It produces characteristic behavior changes, and has a marked blocking effect on interneurons. A striking property is its selective action on the thalamus.

Selling[112,113] reported excellent results in tension headache. Of twenty-seven patients with this complaint, twenty-three either recovered or reported sufficient improvement so that they were no longer concerned with this symptom. He states that Meprobamate has also been found to be of value in the treatment of vascular headache, but the reviewer believes large controlled studies will be required in order to define clearly the proper place of treatment of this type.

Incidentally, all through this review the author has been plagued with difficulties resulting from the variations in definition of the headache syndromes as accepted by various workers. Selling, for example, differentiates tension headache from vascular headache; other workers do not. Also, it has already been pointed out that there is a wide divergence of opinion concerning the relative incidence of histamine cephalalgia and frontal headache (or other vascular headaches). It is to be hoped that there will develop more uniformity of opinion in this matter.

In a personal communication, Fuchs[114] states that he has found Equanil to be useful, especially in patients with the tension variety of headache. He states that these are people who suffer predominantly with nuchal pain; there may be patients with frontal headache, however, who do respond to the drug. The results obtained parallel in general the results in tension states with or without headaches. Kositchek[115] reports two severe allergic reactions, one after the use of Equanil and the other after the use of Miltown. It is, therefore, obvious that Meprobamate may cause sensitization.

We are all familiar with the tremendous interest in and use of these various tranquilizing drugs. They may lessen tension and promote tran-

quility, but it has been found that they may also cause severe depression and even suicide. There is truth in the statement that a person cannot always swap his tensions and anxieties for any medication. It has recently been announced that Congress is expected to authorize federal research into these problems. Therefore, let us not be too quick to substitute a proper medical approach with the simple or casual prescribing of these drugs, which may in the final analysis prove to be not without danger.

In addition to drugs of the ataraxic group, there has been considerable interest in drugs which have a stimulating effect. Medications of the amphetamine type have been used for many years, but are definitely contraindicated in certain individuals. Ritalin® is a new and effective psychomotor stimulant which is used to "step up mood and performance to normal levels," and is a preparation that will probably have a wide use. Our old standby, caffeine, besides being a stimulant is a mild vasoconstrictor.

Vasodilators.—The use of histamine has already been discussed in some detail. Realizing that vasoconstriction precedes the period of increased amplitude of pulsation in vascular headache, various vasodilators such as nicotinic acid have been used. The rationale is that abolition of vasoconstriction would result in the nonappearance of the attack. However, results have been indefinite and therefore these preparations are not in general use. Friedman and Brenner[116] and Vallery-Radot[117] found that 13 per cent of their patients obtained relief from vasodilators.

Many of the ergot derivatives are vasoconstrictors, but the combined ergot alkaloids (dihydroergocornine, dihydroergocristine and dihydroergokryptine) or Hydergine,® act as a vasodilator. Bercel[118] stated that the prophylactic sublingual use of Hydergine exclusively for three months in twenty cases of typical migraine resulted in a reduction of 71 per cent in compounded monthly headache hours, as contrasted to an untreated control period. For another three months the study was pursued while individual attacks were aborted by a number of drugs when they occurred. In this phase of the clinical trial, a reduction of 75 per cent occurred in the number of bouts of migraine. No side reactions were seen. It was stated that Hydergine has effects on both the central and peripheral vegetative apparatus, and it is believed to regulate the vacillating imbalanced vascular tonus of the migraine patient who appears to have cerebral vasoconstriction and increased vacillation of the contractile state of vessels in the headache-free interval.

Grenfell[119,120] describes the use and beneficial effect of Hydergine in hypertension and in headache associated with this condition. Winsor[121] also found that Hydergine was effective in 86 per cent of forty-two patients with hypertensive headache. Kajtor,[122] using Hydergine in ten cases of headache, found that in three the relief of pain was moderate, in four

others it was uncertain, while in three cases pain increased somewhat in intensity. He noted no correlation between the diminution of pain and the decrease of blood pressure, and stated that it was almost without effect in migraine headache, but that it had strikingly good results in vascular headache associated with hypertension. Also, it could also alleviate pain in patients with nonhypertensive vascular headache. Judovich and his associates[63,91] have obtained good results with the use of Hydergine.

Friedman and Von Storch[123] found that vasodilators, even when given in the earliest stage of a migraine attack (vasoconstrictor phase), do not give therapeutic results as specific as when vasoconstrictors (the ergotamines) are used.

Attention has been focused on the state of the autonomic nervous system as a guide to the use of vasoconstrictor or vasodilator therapy.[99] Other authors have found correction of imbalance of the autonomic nervous system conducive to a reduced incidence and severity of a variety of headaches. Still others have found anticonvulsant medication useful as prophylaxis, especially in cases where brain dysrhythmia is evidenced.[75,76] Whether these cases may properly be considered as migraine or epilepsy is a moot question.

It is the opinion of the reviewer that this whole problem requires further analysis. Statistical data on larger groups would be helpful; however, a better understanding of various basic facts and a more uniform approach is essential before final deductions are made. Apparently in vascular headache we are dealing with labile vessels, and the pathologic physiology differs in various persons and at different times. It is becoming increasingly obvious that it is difficult to lay down hard and fast rules which will apply to all patients at all times. Possibly a simple clinical approach will be devised, by means of which we will be able to determine just what medication is indicated at any particular time.

Vasoconstrictors.—General vasoconstrictors, such as epinephrine and ephedrine, have been used in the treatment of vascular headache with varying degrees of success. However they are not specific for cranial vessels, and are not in general use.

Ostfeld and Wolff[124] used Arterenol® (norepinephrine) to reduce the amplitude of pulsations of extracranial arteries. It was given in a dilution of 4 cc of 0.2 per cent solution in a liter of 5 per cent dextrose in water by intravenous infusion, at a rate sufficient to raise systolic blood pressure to 20 to 40 mm Hg. Headaches began to diminish in intensity in ten to sixty minutes, and were eliminated or much reduced in an average time of eighty-two minutes.

Octin,® an aliphatic sympathomimetic drug, relaxes smooth muscle, especially of the hollow organs, while at the same time it exerts a constricting effect on the cerebral blood vessels. It is not uterotonic and is noncumulative. Its use in headache has been studied by a number of

authors.[125-131] It has been found that while Octin often relieves headache, it may also cause some rise in blood pressure in individuals with a tendency to hypertension, or who have a labile vasomotor system. Therefore, it is recommended that a test dose be given intramuscularly in order to determine whether the blood pressure is elevated after its use. Octin may be given by injection or by mouth. The manufacturers suggest that, when given orally, it be combined with a sedative (Bromural®). This combination is known as Valoctin.®

Ergotamine was isolated by Stoll in 1918.[132] The isolation of ergotamine and its less active isomer, ergotaminine, was followed later by the isolation of a whole series of related alkaloids of ergot. Stoll divided ergot alkaloids into three groups, the ergotamine group, the ergotoxine group, and the ergonovine or ergobasine group. The first and second groups are very similar in chemical structure. A detailed chemical analysis would be time consuming, but Stoll shows that the sympathicolytic action of the ergot alkaloids does not result from the lysergic acid portion of the molecule but from the basic fragment to which it is joined by an amide-like linkage.

The ergotamines have been universally accepted as being effective constrictors of cranial vessels. It has been stated that their action is limited to branches of the external carotid artery; however, your reviewer feels that branches of the internal carotid artery also respond to these drugs. It is virtually impossible to discuss all of the investigative work which has been done with the ergotamines, but it must be emphasized that the sum total of all the work on drugs used in the treatment of headache has shown overwhelmingly the efficacy of these preparations in the symptomatic relief of headache. As stated above, the response of the patient with vascular headache to the ergotamines is actually considered to be a diagnostic point. However, in the face of being repetitious, a few points regarding dosage and contraindications are herein summarized:

Ergotamine tartrate (Gynergen®) ½ cc (0.25 mg) subcutaneously or intramuscularly is usually effective, but may be repeated in one-half hour, if necessary. By injection, no more than 1 mg or 2 cc of Gynergen per week is recommended. DHE-45®, dihydroergotamine, is usually as effective as Gynergen and better tolerated, the effective dosage of this preparation being 1 cc (1.0 mg) subcutaneously or intramuscularly in most cases, but may be repeated in half-hour intervals up to 3 cc per attack where necessary. DHE-45 may even be administered intravenously for rapid relief in a serious case, but the intravenous administration of Gynergen is not recommended.

Many patients object to hypodermic injections and for these patients, excellent results can be obtained with these products: Cafergot® tablets (ergotamine tartrate 1.0 mg; and caffeine 100 mg), one or two tablets, repeated every half-hour until relief is obtained, or a maximum of six tablets per attack. Recommended weekly maximum is 10 tablets. Cafer-

got-PB® tablets (ergotamine tartrate 1.0 mg; caffeine 100 mg; pentobarbital 30 mg; Bellafoline® 0.125 mg). This preparation is especially effective in patients who tend to become nauseated and tense during an attack; the dosage is the same as with Cafergot tablets. Cafergot suppositories® (ergotamine tartrate 2.0 mg; caffeine 100 mg) are useful in vascular headaches where early nausea precludes the probability of oral absorption. The dosage is one suppository at the start of an attack, repeated in one hour, to a maximum of three per attack. No more than five suppositories per week are recommended. Cafergot-PB suppositories® (ergotamine tartrate 2.0 mg; caffeine 100 mg; Bellafoline 0.25 mg; pentobarbital 60 mg) are useful in vascular headaches complicated with early and severe nausea or vomiting and nervous tension. The dosage is the same as with Cafergot suppositories.

Other ergotamine combinations are now commercially available, but lack of space prevents a detailed description. One of these is Wigraine®, the composition of which is ergotamine tartrate 1.0 mg; caffeine 100 mg; belladonna alkaloids, levo-rotatory 0.1 mg; and acetophenetidin 130.0 mg.

Contraindications of ergotamines: Peripheral vascular disease, angina pectoris, organic heart disease, hypertension, impaired renal or hepatic function, pregnancy and septic states associated with intravascular foci. The excessive use of ergotamine is ordinarily not recommended because of the fact that ergot derivatives are cumulative; also there is the possibility of a "rebound" type of reaction. However, many have exceeded the suggested weekly maximum without difficulty.

It should be emphasized that the ergotamines must be used as early as possible in an attack. If the medication is used after the headache is well established, therapeutic results are not as clearcut. Edema of the vessel walls increases during the headache episode, rendering the response to the ergotamines more difficult. These preparations should be used at the onset of the attack, and should not be used prophylactically. All too often the reviewer has seen prescriptions calling for one Cafergot tablet three times a day; this just does not make sense.

Unfortunately, vascular headaches often manifest themselves when the patient awakes. This means that they may have begun at some time during the night. The taking of an ergotamine, as stated above, may be less effective when the attack has been present for several hours. It has even been suggested that such a patient not allow himself to sleep heavily for long periods and in some cases it may be helpful to break up the hours of sleep into two or three divisions. However, it has been observed that headaches frequently appear during the time of relaxation, such as on a week end, or, as stated above, during sleep.

It must be remembered that the ergotamines are vasoconstrictors, and any vasoconstrictor may have a "rebound" effect. Many patients have used the ergotamines far in excess of the recommended dosage for long periods of time, as reported by several authors. Ergotism is rare, but

vascular symptoms (especially in the peripheral vessels) may appear and may indicate cessation of its use. Peters and Horton[133] called attention to the fact that withdrawal headaches may appear when the ergotamines are discontinued. This is similar to the well recognized "caffeine withdrawal" headache which may appear when the use of coffee is stopped. These authors state that dihydroergotamine (DHE45) is less toxic, and suggest that too frequent use of the ergotamines should be avoided. The same authors report a number of patients who received 1,000 and 1,500 mg of ergotamine over a six-year period without evidence of ergot poisoning.

Friedman, Brazil, and von Storch[134] call attention to the fact that in some patients the use of ergotamine relieves the headaches for which it is administered, but at the same time leads to an increased frequency of these headaches. However, it must be stated that only five patients of this type were seen in a very large group. The occasional occurrence of this reaction may be attributed to the "rebound" effect which has already been discussed. Therefore, an occasional reaction of this type may possibly be seen in a patient who uses the ergotamines in excess of the recommended dosage.

Gangrene due to ergotism rarely occurs; however it has been reported.[135-137] Friedman et al[134] state, however, that in over 1,000 patients no signs of toxicity have appeared.

Despite the contraindications, dangers of overdosage, and the necessity for correct timing, the ergotamines are more effective than any other medication for the symptomatic relief of all varieties of vascular headache, including the frontal type.

Prophylactic Treatment.—Friedman[138] states that a small number of headache patients respond well to the prophylactic use of Mesantoin® or Dilantin.® The presence of an abnormal electroencephalogram suggests the use of an anticonvulsant as a preventive type of medication.

Hilsinger[139] points out that autonomic imbalance may be a contributing factor in vascular headache, and suggests the use of a preparation which will "dampen" the autonomic nervous system. Such a drug is Bellergal® which contains a sympathetic inhibitor (ergotamine tartrate), a parasympathetic inhibitor (Bellafoline®), and a central sedative (phenobarbital). Wittich[140] and Steele[141] report good results with this preparation. Steele states that the usual dosage was three tablets daily, except for withdrawal of treatment for one week out of every four to six weeks, in instances of prolonged therapy. Bellergal® spacetabs, being double strength and having a duration of action of ten to twelve hours, should provide excellent sustained control with convenient twice daily dosage.

Various other medications may at times be used to lessen the incidence of headache. Besides the ataraxics, sedatives may be used in selected cases where the factor of emotional tension is great.

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The reviewer has prepared the following diagram which may be helpful in the symptomatic management of headache.

PREFERRED SYMPTOMATIC TREATMENT OF HEADACHE

HEADACHES	1	2	3
A. Vascular Headaches			
Migraine	Vasoconstrictors	Nonnarcotic analgesics	Antihistamines
Occipital headache (not myalgia)	Vasoconstrictors	Nonnarcotic analgesics	Antihistamines
Generalized headache	Vasoconstrictors	Nonnarcotic analgesics	Antihistamines
Frontal headache	Antihistamines	Vasoconstrictors	Nonnarcotic analgesics and nose-drops
Histamine cephalalgia	DHE45		
B. Myalgia	Nonnarcotic analgesics	Heat and massage	
C. Combination Headache (Vascular plus Myalgia)	Vasoconstrictors plus nonnarcotic analgesics	Heat and massage	Antihistamines

†Columns 1, 2 and 3 indicate first, second and third choice of treatment.

THE PREVENTION OF HEADACHE

It should be the goal of the physician to manage all causative factors which may play a role in the production of headache. Various specialized types of medical examination and treatment may be specifically indicated, such as consultations with an ophthalmologist, otorhinolaryngologist, internist, orthopedic surgeon, neurologist, neurosurgeon, endocrinologist, dentist or others. In addition to usual laboratory procedures, x-ray, electroencephalogram, and other procedures may be indicated. The reviewer feels that the most important basic fields of approach in many cases are through the psychiatrist (and occasionally the analyst) and the allergist. Ouer[147] also cites the necessity of prevention of attacks, as well as symptomatic relief of the individual attacks.

Emotional or stress factors have been discussed, and must be properly appreciated. The personality problems which may be present are at times associated with headache. It has been repeatedly stated that the migraine sufferer is a perfectionist—he may be very meticulous, very careful, and try to excel in whatever he does. This means that he is under considerable tension whenever he is doing any kind of work, especially mental work. However, it is undoubtedly true that most human beings have personality problems of one type or another, and that most of us have specific problems associated with our work, personal factors and general makeup. Our studies may be misleading, and the patient whom we regard as having an allergic type of headache may also have definite difficulties associated with these personality problems. A consultation with a psychiatrist or neurologist should be obtained whenever indicated.

It has also been clearly shown that allergy or an antigen-antibody type of reaction may, in many cases, be the precipitating cause of headache. Therefore, as we become better allergists more and more beneficial results will be obtained through improved diagnostic procedures with resultant

better appreciation of all possible causes. To further illustrate this point, in the past we thought that many allergic troubles were due to nonspecific factors (such as weather, emotions, fatigue) that we now know are definitely and specifically due to sensitization to some antigen. The list of common antigens is becoming quite long, and includes pollen, inhalants, foods, molds, fungi, and bacteria.

The importance of inhalant sensitizations as a cause of nasal reactions is generally appreciated. Since nasal changes are so often associated with headache, this aspect of the problem often calls for evaluation[15] and many cases of headache will be benefited by proper avoidance measures and hyposensitization. Every allergist has seen patients who have improved concurrently with treatment which follows closely the improvement in nasal symptoms. A careful discussion during the taking of the patient's history will often reveal the fact that he does present chronic or seasonal nasal changes. Even minor nasal mucosal edema may be associated with headache. In the experience of the reviewer, allergy to house dust is the most frequent cause of such nasal changes, but in many individuals infection or bacteria (especially staphylococci) may play an important role. At times hyposensitization with a bacterial vaccine may be helpful, and organisms for the culture are best secured from the region of the antrum. A stock vaccine may be used at the same time.

We are all aware of the fact that sensitization to foods may precipitate headache. Unger and Unger,[38] as stated above, found that 80 per cent of fifty-five patients were either completely or almost completely relieved of headache by the detection and elimination of causative foods.

Kaufman[142] also has made a detailed study of food-induced allergic headaches, and states that there are two major varieties of food allergy, the fixed and the variable. In the first type, a constant oral threshold amount of the offending food may regularly precipitate headache after a fixed latent period. In the second type, tolerance for the food varies from time to time. The patient may be sensitive to more than one food. He also notes that in diagnosis the patient may be given one suspected food at a time in order to see if symptoms are produced. The reviewer is in accord with this statement; however, we must take into consideration the influence of the "power of suggestion." All too often patients suspect allergy to foods, but this may be disproved by careful objective studies, such as by disguising the food, or even by the feeding of foods through a stomach tube. In this way, the patient may not know just what food he is receiving. By this means it is possible at times to disprove faulty conceptions which may be present in the minds of both the patient and physician.

Kaufman[142] also states that there may be sudden gain in weight following ingestion of a single oral threshold amount of an allergenic food.

Food diaries have been used to some extent to determine food sensitizations. A number of years ago Vaughan[143] called attention to the use of

the leukopenic index, dependent on the postprandial drop in the total white blood cell count which followed the ingestion of an antigenic food. However, the performance of this procedure is obviously difficult, expensive and time consuming.

Some allergists feel that skin testing for foods is extremely inaccurate, and have therefore discontinued this phase of the allergy survey. However, it is also felt by many that there is a certain amount of information which may be so gained. The combination of a careful history, skin testing and then direct tests with suspected foods will usually give the necessary information. A popular procedure is to place the patient first on a diet which is restricted to foods which are well tolerated, and then to add a new food to the diet each day. A minimal amount of a new food should to be taken at the first two feedings because of the possibility of a severe reaction.

THE INTEGRATED APPROACH

We have seen that there are several types of vascular headache, and that there may be several causes of this condition which may be present in the same individual at the same or at different times. The management of one cause of headache may not give adequate relief, if other factors are not properly appreciated. Therefore, the proper study of the headache patient calls for an integrated approach, in which all these factors are viewed from the general or "over-all" viewpoint. The management of the patient from the viewpoint of one particular specialty may be unsatisfactory. Since headache is such a common complaint, it is predicted that more workers and clinics will devote special attention to the problem.

In this review the writer has attempted to be as definitive as possible. There are so many conflicting views regarding certain aspects of headache, that it is necessary for us to orient ourselves properly in order that our progress will result in increased benefits for the untold millions who suffer with headache. In the words of a friend, we have tried to "uncomplicate" a very complicated subject.

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143. Vaughan, W. T.: Practice of Allergy. St. Louis, Mo.: C. V. Mosby Co, 1939.
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How Your College Works

THE ANNALS OF ALLERGY

It is the chief function of the ANNALS OF ALLERGY to advance either knowledge or understanding of any aspect of the field of allergy. From the simplest advertisement describing a new drug to the most erudite paper concerned with immunologic relationships, every word, except from some of the news items and the obituaries, moves forward in this one direction.

In actual practice, the subjects of the Progress Reports are chosen at the annual meeting of the Editorial Board. The members of the Board assume this responsibility, except in those rare cases when an authority in a special field, who is not a member of the Board, is invited to contribute, Each year at least one, and sometimes two, such reports are so chosen. Every important aspect of allergy is covered from the date of the last published report on the same subject. Any Fellow of the College who notifies the Editorial Board that he plans to do a review of any pertinent material not so far published is always welcomed and given a place in the schedule tentatively fixed for the ensuing twelve to eighteen months.

The majority of the papers published have been presented at the annual general session, the sections, and sometimes the Graduate Instructional Courses. Other papers are sent in by workers in the field. When members of the Editorial Board learn of work in progress, they invite the investigator to submit papers for publication in the ANNALS. Any worker in allergy or in an associated discipline, independent of membership in the College, may submit a paper for consideration.

All papers, no matter how obtained, are read with an eye to knowledge of previous work in the same field, proper acknowledgment of such work, accuracy of quotation, pertinence of subject matter, and validity of experimental pattern. Practicality and usefulness are the chief criteria for acceptance. Our readers are not interested in the "fourth decimal place" unless it can be proven to be important.

The bibliography is spot-checked for accuracy. The paper is then sent separately to two editors, each of whom has proven himself an expert in the subject. Publication can be expedited when both an original and a carbon copy are submitted. Neither editor knows that the paper has gone to the other. Each independently returns his comments to the Editorial Office. If both agree that the paper is worthy of publication "as is," it is mailed (often the same day) to the publisher. If either editor uncovers an inconsistency or is not content with any scientific or literary aspect of the paper, he can request that it be rewritten. His exact comments are returned with the paper to the author for the author's own opinion. If the differences are major, the paper is resubmitted to two

other editors. If the differences are minor, the author usually rewrites the paper making it longer or shorter, more lucid or more complete, as suggested.

When both the editors reject a paper, the reasons for its rejection are sent to the author. Occasionally an author differs with the editors, in which case the paper is resubmitted. Whenever one editor rejects a paper acceptable to the other, the paper is sent to two new members of the Editorial Board, neither of whom knows of the initial two opinions. If both report the paper as acceptable, the vote of three to one is sufficient for publication. When both reject the paper, the vote of three to one against publication is equally valid. If and when there is one acceptance and one rejection, the paper goes to a third set of two editors. Opinions are remarkably consistent and usually unanimous. But, some papers do require a reading by six editors. If the score remains even, the Editor-in-chief casts the deciding vote.

In the past, the format of papers has been the subject of discussion. The editors of almost all journals insist that papers be submitted in a specific form, easily understood by consulting recent issues of the journal in question. Each journal has a pattern to which it expects the submitting author generally to conform. Nowhere is this seen in its more rigid conventional pattern than in the publication of the bibliography.

The *J.A.M.A.* uses the Cumulative Index type of reference with each reference given consecutively in the text for printing at the foot of each column. No more than eighteen references are permitted for any one paper, the length of which is limited to 5,000 words. The New York Academy of Sciences gives the author two choices, alphabetically by authors, with no numbers, as for example:

Klotz, I. M., P. Griswold and D. M. Gruen. 1949. Infrared Spectra of Some Proteins. J. Am. Chem. Soc. 71:1615, or numbered consecutively in order of appearance in the text:

15. Porter, K. R., A. Claude and C. F. Fulham. 1945. A Study of Tissue Culture Cells. J. Exptl. Med. 81:233.

In the past, the ANNALS OF ALERGY has requested that the references in the bibliography of papers submitted be arranged alphabetically and numbered consecutively. As, for instance:

12. Smith, J. E.; Jones, M. A.; and Walker, E. B.: A new theory for the explanation of allergic phenomena. Ann. Allergy, 16:231-261 (May) 1951.

Every important statement should be given bibliographical reference, and, naturally, the bibliography should list no references not keyed to the paper.

In the past this has led to minor difficulties. Whenever the paper so keyed was rejected for the reason that it was more appropriate in another journal, the paper had to be rewritten. Papers sent to the ANNALS for the same reason also had to be retyped and rekeyed to conform.

HOW YOUR COLLEGE WORKS

With this issue, the Editorial Board wishes to announce a change in policy. Since the chief purposes of the ANNALS are communication to its readers and the convenience of the authors, papers will be acceptable for publication as regards the form of the bibliography whenever it conforms to any of the patterns now generally accepted and is, of course, consistent within itself. Readers' preferences, however, are for full names of all authors, full titles of all papers with the journal, volume, page or pages, and the year of publication, arranged alphabetically or consecutively.

The length of the paper and the completeness of the bibliography should be determined by the importance of the subject matter and what it warrants.

News items may be sent in by individual members concerning their own activities of general interest. Secretaries of local allergy societies are invited to mail in notices of meetings and programs and the results of their annual elections. These must be received at least sixty days before the date of the issue in which they are to appear. For example, for certain publication in the January-February issue, receipt is required before November first, although room can sometimes be made for late notices of importance.

Obituaries are written by friends of the deceased Fellow and are published as early as possible.

Subject to the same rules of approval as papers, editorials may be submitted by any Fellow. Book reviews are similarly acceptable. Entries for "Papers of Interest," giving full bibliographic details with one or two qualifying notes, are invited. Any Fellow who would like to see an "Historical Document" republished as space permits may bring it to the attention of the editors. Quotations for "Fillers" are always welcome.

Any Fellow who has any suggestions as to how the ANNALS can be made more useful or interesting to its readers should not hesitate to write to the Editorial Office.

The ANNALS OF ALLERGY belongs to the College and to its Fellows. It is *their* journal. It can only be published to suit them if they will either send in papers or tell the Editors what it is they want to see in its pages.

LABORATORY MANUALS FOR SALE

Dr. Stephen D. Lockey still has available a few copies of the Manual of Office and Laboratory Procedures, which was used in his laboratory course during the Twelfth Annual Graduate Instructional Course in Allergy at the Hotel New Yorker, New York City, April 15-17, 1956. These manuals can be purchased for $4.00 each, plus twenty-five cents postage. All profits from the sale of these manuals go directly into the treasury of the College. Books may be purchased directly from Dr. Stephen D. Lockey, 60 North West End Avenue, Lancaster, Pennsylvania.

Papers of Interest

Simmons, R. D. G. P.: The effect of non-medicamentous enclosure and "dermatologic rest" on eczema. J. Invest. Dermat., 25:365 (Dec.) 1955.

A new form of "dermatological rest," plaster of paris bandages with no ointment, achieved remarkable results in the treatment of eczema of 100 patients.

Seal, J. R.: Reactions to influenza vaccine. U. S. Armed Forces M. J., 6:1559 (Nov.) 1955.

At three Naval Training Centers and two Marine Corps depots, 0.05 per cent of those immunized with influenza virus vaccine suffered reactions necessitating hospitalization.

Adams, C. R.: Agranulocytosis and severe leukopenia after chlorpromazine hydrochloride. Brit. M. J., 1:1087 (May 12) 1956.

Review of the literature and case report of a severe case of agranulocytosis with severe leukopenia due to chlorpromazine hydrochloride.

Dawson, C. R.: The chemistry of poison ivy. Trans. New York Acad. Sc., 18:427 (March) 1956.

Immunity to poison ivy follows intramuscular injection of PRC (3-pentadecylcatechol).

Welch, H.: Antibiotics in fluid market milk. Third nation-wide survey. Antibiotics and Chemotherapy, 6:369 (May) 1956.

Penicillin was found to be present in 5.9 per cent of the samples. One per cent contained other antibiotics.

Katz, S., and Mast, G. W.: Choline theophyllinate—a new xanthine derivative. A review. J. Am. Geriat. Soc., 4:251 (March) 1956.

The drug possesses an unusually low incidence of gastric irritation, and is considered one of the drugs of choice for the treatment of chronic bronchial asthma.

Schwartz, E., et al: The use of antitussives in the management of bronchial asthma. Am. Pract., 7:585 (April) 1956.

A review of the antitussives useful in the respiratory distress associated with wheezing.

Black, A. P.: A new diagnostic method in allergic disease. Pediatrics, 17:716 (May) 1956.

Dried allergens are placed on microscopic slides. The patient's plasma-leukocyte suspension is added. The slides are petrolatum sealed and kept at 37° C. Sensitivity is evidenced by a progressive cytotoxic lethal effect on the leukocytes, which is absent in the controls.

Martin, W. J. et al: Novobiocin: Further observations. Antibiotic Med., 2:258 (April) 1956.

Novobiocin remains in the blood for long periods of time. Results were encouraging in thirty-four patients studied clinically, but allergic dermatitis was common.

Brown, E. B.: Intramuscular crystalline khellin for management of chronic bronchial asthma. Am. Pract., 7:609 (April) 1956.

Pure crystalline khellin suspension in isotonic saline injected intramuscularly was effective in the symptomatic control of bronchial asthma, the patients being studied over a period of four years.

Wolf, R. L., and Brown, L. T.: Primary atypical nonbacterial pneumonia: An evolution of the efficacy of antibiotic therapy in 118 cases. Arch. Int. Med., 97: 593 (May) 1956.

Chlortetracycline, erythromycin, oxytetracycline and tetracycline do not shorten the duration of pneumonitis in primary atypical nonbacterial pneumonia in Navy personnel.

Singer, J. I., and Merlis, S.: Skin sensitivity to chlorpromazine. New York State J. Med., 56:1285 (Apr. 15) 1956.

A contact dermatitis is reported in hospital personnel.

Lipman, D. G.: Antihistamines and hypertension. Preliminary report on chlorprophenpyridamine maleate. J. Am. Geriat. Soc., 4:286 (March) 1956.

In sixteen patients with persistent hypertension of nine and one-half years' average duration, treatment with Chlor-Trimeton Repetabs® lowered the blood pressure. All had been refractory to previous types of treatment. The effect was therefore considered due to the antihistaminic agent.

Weinstock, I., and Albin, M. B.: Auto-observation of a near fatal penicillin reaction in a physician. New York State J. Med., 56:1825, 1956.

Vivid description of the sensations in such an accident.

PAPERS OF INTEREST

May, R. H., and Voegele, G. E.: Parkinsonian reactions following chlorpromazine and reserpine. Arch. Neurol. & Psychiat., 75:522 (May) 1956.

The authors suggest that identical areas of the central nervous system are affected by chlorpromazine and reserpine, because four patients to whom the drug was given alone gave the appearance of having the typical Parkinsonian syndrome.

Weijlard, J.; Orohovats, Peter D.; Sullivan, A. P.; Purdue, G.; Heath, F. K.; and Pfister, K.: A new synthetic analgesic. J. Am. Chem. Soc., 78:2342 (May 20) 1956.

The authors describe a new analgesic compound which is twice as active, dose for dose, as Demerol, and almost equal to morphine in its analgesic qualities. Of interest is the fact that the side reactions are milder than those of Demerol. It possesses, in addition, anti-acetylcholine, antihistaminic, and antitussive qualities.

Shands, W. C., and Johnston, J. H: Anaphylactic shock from intrapleural streptokinase-streptodornase. J. Thoracic Surg., 31:320-323 (March) 1956.

A severe case of near-fatal anaphylactic reaction following a third intrapleural injection of streptokinase-streptodornase is reported.

Siegal, S.; Goldman, J. L.; Arnold, L. M.; and Herschberger, C.: Sinus disease, bacterial allergy, and bronchial asthma. Arch. Int. Med., 97:431-441 (April) 1956.

This study appears to warrant the conclusion that sinus infection is not a primary cause of asthma but rather a complication superimposed on altered sinus membrane.

Noajin, R. O.: The dermatologic management of pruritus. South. M. J., 49:149-155 (Feb.) 1956.

The three most effective agents for local use are hydrocortisone and fluorohydrocortisone ointments, menthol and/or phenol in shake lotions, and cool, wet dressings. The three most effective systemic agents are the antihistamines, the corticosteroids, and chloral hydrate and/or phenobarbital.

Brenner, J. J., and Lubart, A.: Subacute bacterial endocarditis in a penicillin-sensitive patient successfully treated with ACTH, Chlor-Trimeton, and penicillin. New York State J. Med., 56:1662, 1956.

Penicillin in rapidly increasing doses (and during the first period admixed with Chlor-Trimeton) was tolerated after ACTH therapy had been initiated after a previous attempt to "desensitize" with penicillin plus Chlor-Trimeton had failed.

Baer, R. L.: Current views on atopic dermatitis. New York State J. Med., 56:1664, 1956.

Succinct presentation of the "orthodox" dermatologic view—worth while reading be it only to disagree on the etiologic approach. The average allergist can certainly learn a great deal about the fine art of local therapy from the dermatologist.

Sternberger, L. A.; Feinberg, S. M.; and Clarke, M. E.: Studies on nonprecipitating antibody. J. Exper. Med., 103: 523, 1956.

The conversion of nonprecipitating antibody to a precipitin-like material *in vitro*.

Sehon, A. H.; Harter, J. G.; and Rose, B.: The localization of skin-sensitizing antibody in the sera of ragweed-sensitive individuals by electrophoresis. J. Exper. Med., 103:679, 1956.

Found in gamma globulin fraction by starch electrophoresis.

Weissman, H.: Bronchogenic carcinoma and pulmonary tuberculosis. Problems in diagnosis with special reference to antituberculous chemotherapy. Am. Rev. Tuberc., 73:853 (June) 1956.

The two disorders may coexist or mimic each other. One means of differential diagnosis is the therapeutic test with antituberculosis chemotherapy.

Respiratory diseases. Upper respiratory virus infections. Lancet, 2:844 (June 2) 1956.

An excellent review of the subject.

Rantz, L. A., and Rantz, H. H.: Antibiotics: Sensitivity of various clinically important bacteria to seven antibiotics. Arch. Int. Med., 97:694 (June) 1956.

Various strains of *Staphylococcus albus, Staphylococcus aureus, Streptococci, E. coli, B. proteus,* and other bacteria were tested against penicillin, streptomycin, oxytetracycline, chloramphenicol, erythromycin, neomycin, and polymixin. Many bacteria are now more resistant to antibiotic agents than they were five years ago.

Letter to the Editor

To the Editor
ANNALS OF ALLERGY

Dear Sir:

The report of Ratner and Flynn on the "Anaphylactogenic Properties of Piperazine Citrate" (Ann. Allergy, 13:176-179, 1955) calls attention to a clinical problem in which we have long been interested and have been attempting to study, i.e., urticaria and angioedema occurring during the course of therapy directed against parasitic infection. It is felt that the points raised are of sufficient importance to make our observations noteworthy in this regard.

We are in complete agreement with the conclusions of Ratner and Flynn. Their experimental studies, demonstrating a lack of antigenicity of piperazine citrate in guinea pigs, would tend to parallel the results of clinical observation in failing to establish unequivocal proof or documentation of sensitizing properties of this drug in large series of human patients similarly treated. Though urticaria has been observed in patients treated with piperazine citrate for *Enterobious vermicularis* and *Ascaris lumbricoides* infections, and sensitivity to this drug has been suggested as an etiologic explanation, the incidence of this symptom has been so low as to justify alternate explanations of incidental nonspecific or undetermined factors or other coexisting allergic reactions producing this manifestation.

Among other possibilities offered to explain the etiology of an urticaria in this situation, we have previously suggested that of the development of sensitization to the helminthic protein or a "foreign protein" reaction following its tissue absorption. This possibility has also been recently mentioned by Rachelson and Ferguson (Am. J. Dis. Child., 89:346-349, 1955). Certainly the antigencity of somatic proteins of helminthic parasites (e.g. *Ascaris)* has been repeatedly demonstrated experimentally. Urticaria and angioedema are prominent symptoms occurring during the course of the tissue invasive phase of such parasitic diseases as trichinosis and schistosomiasis, and anaphylactic shock may also occur after the absorption of fluid from a ruptured Echinococcus (hydatid) cyst. The following observations recorded by us during the course of treatment of adults and children for *Enterobius vermicularis* infections may be of interest in contributing information to an understanding of this still unestablished point:

1. The occurrence of urticaria in the effective treatment of *Enterobius vermicularis* infection is not limited to any one particular drug. It has been seen with methylrosaniline chloride, oxytetracycline, parabenzylphenylcarbinate and piperazine citrate.

2. Once urticaria has appeared during the course of therapy with any one of the above listed drugs, recurrence in the same individual is not limited to the readministration of the same drug. If the first course of therapy with one agent is not completely satisfactory in totally eradicating the parasite or if treatment is being given for reinfection, urticaria tends to recur during a second course of therapy with the administration of either the same or an unrelated drug.

3. The onset of urticaria and angioedema seem to occur more commonly toward the middle or end of the first course of therapy. This would seem to coincide with a time expected for the killing of large numbers of parasites. Though only a matter for speculation, this would seem to offer the first opportunity for the tissue absorption of foreign protein from the dead worms whose previous localization had been limited to the lumen of the intestinal tract. This time-effect relationship resembles the exacerbations of urticaria described in the amebacidal therapy of patients infected with *E. histolytica* (Cohen, S. G., and Criep, L. H., Am. Pract., 1:246-252, 1950). Both these situations may be similar in mechanism to the Herxheimer reaction seen in the antispirochetal therapy of syphilis, when symptoms are caused by

the sudden absorption of large amounts of foreign protein derived from the recently killed spirochetes.

4. Urticaria on occasion has appeared in association with *Enterobius vermicularis* infection in such clinical relationship as to suggest that the urticaria represented an unusual symptom of the intestinal parasitic infection based upon the development of sensitization to the somatic protein of the worm. During this unusual situation there usually occurred an exacerbation of the urticarial lesions during the middle or toward the end of the course of effective antihelminthic therapy.

5. The urticaria, once developed, seemed to depend upon the efficacy of the drug and the resultant destruction of the parasites. The urticaria often subsided spontaneously despite continuation of the drug after adult parasites were no longer observed or ova could no longer be demonstrated on anal smear. Urticaria did not appear in the patient during a trial readministration of the drug in question following successful eradication of the parasite.

6. The urticarial reaction has been observed in both atopic and nonatopic individuals under treatment for *Enterobius vermicularis* infections. It is not known whether the presence of associated allergic manifestations influences the development of this symptom.

The lack of controlled studies and insufficient statistical data do not warrant acceptance of any of the above beyond the original intention of recording simple clinical observations. We are attempting to overcome certain technical difficulties in the preparation of an appropriate *Enterobius* protein extract for the purpose of skin testing. Only by accepted methods for detecting reagins or other circulating antibodies in *Enterobius* infected individuals with and without urticaria and by the study of large series of these case reports can the role of hypersensitivity reactions in this condition be properly evaluated.

SHELDON G. COHEN, M.D.
Chief, Allergy Service
JOSEPH ROBINSON, M.D.
Chief, Pediatric Service

Mercy Hospital
Wilkes-Barre, Pa.
April 26, 1956

In Memoriam

JOHN PETERS

It is with regret that we announce the sudden death on January 29, 1956, of John Peters, Oak Park, Illinois, who suffered a coronary occlusion twenty-four hours previously.

Dr. Peters was born April 15, 1889, at Winnipeg, Canada. He attended Crane College and the Chicago College of Medicine and Surgery where he received his medical degree in 1912. He interned at the Norwegian Deaconess Hospital. He practiced thirty-three years in Maywood, Illinois, specializing in allergy, and had an office in Oak Park for the past twenty-two years. Dr. Peters was associate clinical professor of medicine at Loyola University from 1928 to 1940, was a Fellow of the American College of Physicians, the American Academy of Allergists, and the American College of Allergists. He was a past president of the Chicago Society of Allergy. He was likewise a member of the Chicago Medical Society, Illinois Medical Society, and the American Medical Association.

Last December, Dr. Peters was elected as president of the staff of the Oak Park Hospital, where he had been on the staff for forty-three years. The last year or two, he was in the throes of activity pertaining to the foundation for retiring doctors.

Dr. Peters is survived by his wife, Lillian; two daughters, Hortense Neimark and Muriel Davis; two brothers and a sister, all of Chicago, to whom the officers and members of the College extend their sincere sympathy.

News Items

THE AMERICAN COLLEGE OF ALLERGISTS
Thirteenth Postgraduate Course and Congress

The Palmer House, Chicago, Illinois
March 17-22, 1957

The Thirteenth Annual Postgraduate Course, March 17-22, 1957 with Dr. Merle Moore, Chairman, will be held at the Palmer House in Chicago, Illinois. A tentative program has been set up subject to the usual minor last minute changes. The complete program will be published in the November-December issue of the ANNALS OF ALLERGY. A News Letter giving additional details is on its way to all College members.

The Thirteenth Annual Postgraduate Course will begin on Sunday morning, March 17, at 9:00 A.M.; the morning being given to Allergic Coryza, with emphasis on symptomatology, etiology and therapy, specific and nonspecific. Every aspect of the subject of Nasal Allergy will be covered. The afternoon will be given to formal instruction in all types of Allergic Dermatoses, followed by an informal panel, and question and answer period. Adequate time for discussion will be allowed.

On Sunday evening, March 17, the participants will be able to confer with the instructors on questions of office procedures, and there will be practical demonstrations. Both of these courses will be under the direction of Dr. Stephen D. Lockey.

On Monday morning, March 18, the subject of Bronchial Asthma will be studied, and discussion will be from the point of view of practical diagnosis and treatment. Included will be papers on specific therapy, the use of steroid and non-steroid drugs, mechanical, physical, and climatologic aids.

On Monday afternoon, Miscellaneous Allergy will be given emphasis, with expert instruction available in those types of allergy which include reaction to drugs, insects, food, and physical agents.

On Sunday and Monday from 12.00 A.M. to 2:00 P.M. there will be continued Practical Demonstrations and Office Procedures.

On Monday evening at 8:00 P.M. there will be an informal get-together of all registered students, the instructors, and the College officers for a Beer-and-Buffet Supper. There will be no separate charge for this supper to physicians who have registered for the full course, the fee for which is $50.00 for nonmembers of the College and $20.00 for Associate Fellows and Fellows of The American College of Allergists. Others who wish to attend may obtain tickets ($5.00) at the registration desk until 2:00 P.M. on Monday, March 18, 1957. Although at the New York meeting there was a separate charge, and the food was limited to sandwiches (the beer being unlimited), the session was so enjoyable that it went on until almost midnight. It is being repeated by request.

The session on Tuesday represents a departure from the previous Instructional and Postgraduate Courses. It will be based upon highly advanced, but fundamental material. Speakers, by invitation, will discuss "The Allergic Mechanism," each from the point of view of his own specialty. The Chairman of Advanced Postgraduate Studies for 1957 is Dr. Morris Kaplan. Beginning at 9:30 A.M. there will be five thirty-minute papers, and beginning at 2:00 P.M. four more, with a question and answer period beginning at 4:00 P.M. (Registration fee is $10.00 for this one-day session only.)

A Cocktail Party for registered students and members of the College is planned for Tuesday evening. Wives of both members and students are welcome.

The General Scientific Session will begin on Wednesday, March 20, at 9:00 A.M. Papers will be limited to twenty minutes followed by ten minutes for discussion.

Thursday morning, March 21, will be devoted as much as possible to papers by Associate Fellows seeking advancement to full Fellowship, and to the winners of the Bela Schick and Clement Von Pirquet Awards.

The guest speaker will be introduced at 2:00 P.M. and the Business Meeting will commence as usual at 4:00 P.M. The cocktail party at 6:30 P.M. will be followed by the annual banquet at 8:00 P.M.

All day Friday, March 22, will be given to the sectional meetings. The sections on Ophthalmologic and Otolaryngologic Allergy and on Dermatologic Allergy will meet concurrently from 9:00 A.M. to noon. The Psychosomatic and Pediatric Sections will meet concurrently from 2:00-5.00 P.M.

Although each day from Sunday to Thursday (12:00 A.M.-2:00 P.M.) will be devoted to Office Procedures and Practical Demonstrations, a new section on Technology will have its first meeting on Friday afternoon. It will be concerned with problems of technique as applied to the practice of allergy. Formal papers, by physicians interested in this field, will discuss the preparation, purification, and standardization of extracts. Technologists, technicians, and members of the College are welcome to attend and participate, especially during the question and answer period.

The deadline for papers for the scientific session has been advanced to *October 1, 1956,* so that the finished program can appear in the November-December, 1956, issue of the ANNALS OF ALLERGY, instead of in the January-February, 1957, issue. Abstracts of papers for presentation at the general session, giving exact title, reading time, and other pertinent facts should be in the hands of the Over-All Chairman, Dr. Orval R. Withers, 428 Plaza Parkway Building, Kansas City, Missouri, as far in advance as possible.

L'HOPITAL BROUSSAIS, PARIS, SCHEDULES SYMPOSIUM ON ALLERGIC DISEASES

A symposium on allergic diseases will be held at l'Hôpital Broussais, 96, rue Didot, Paris XIVe., France, from October 15-25, 1956. The cost of the course is 5,000 francs for the lectures and 10,000 francs for both lecture course and practical demonstrations. Applications should be sent, and checks made out, to the Clinique Médicale Propédeutique de l'Hôpital Broussais. As the number of enrollments is strictly limited, applications should be sent in as soon as possible. The program for the ten-day course is as follows:

Monday, October 15

Morning Session—9:30 A.M.

Introduction.....Professor Pasteur Valery-Radot
Experimental Anaphylaxis.....Dr. B. N. Halpern
Generalizations on Humoral Allergy and Tissue Allergy.....Professor Valery-Radot

Afternoon Session—2:30 P.M.

Practical Demonstrations: Study of Anaphylactic Shock in Animals (Dog, Guinea-pig, Rabbit, and Rat). Arthus Phenomenon (Serum and Penicillin)
Dr. B. N. Halpern

Tuesday, October 16

Morning Session—9:30 A.M.

Respiratory Allergy: Pollens, Spasmodic Coryza, Asthma, Löffler's Syndrome
Professor Valery-Radot
Clinical Demonstrations (Presentation of Patients).....Dr. Blamoutier

Afternoon Session—2:30 P.M.

Asthma Provoked by Specific Antigens and Drugs. Protective Action of the Antihistamines and Alkaloids.....Dr. B. N. Halpern

Wednesday, October 17

Morning Session—9:30 A.M.

Pathologic Anatomy of Allergic Lesions.....Professor Gauthier-Villars
Allergy of the Alimentary Tract.....Professor Valery-Radot
Allergic Manifestations of the Digestive Tract.....Professor Valery-Radot

Afternoon Session—2:30 P.M.

The Pharmacodynamics of Antihistamines. Action on the Permeability of the Capillaries. Histamine shock. Shwartzman's Phenomenon. Koch's Phenomenon .....Dr. B. N. Halpern

Thursday, October 18

Morning Session—9:30 A.M.

Dermatologic Manifestations of Humoral Allergy.....Professor Valery-Radot
Allergic Dermatitis.....Dr. Edward Sidi
Renal Allergy.....Professor Valery-Radot

Afternoon Session—2:30 P.M.

Immunologic Procedures.....Dr. B. N. Halpern
Biologic Dosage of Histamine. Role of Mastocytes in the Liberation of Histamine .....Dr. B. N. Halpern

Friday, October 19

Morning Session—9:30 A.M.

Articular Allergy.....Professor Valery-Radot
Cardiovascular Allergy.....Professor Valery-Radot
Allergic Diseases of the Blood.....Dr. Bernard-Dreyfus

Afternoon Session—2:30 P.M.

Chemistry of Antigens and Antibodies.....Dr. Grabar
Methods of Dosage of Antibodies.....Dr. Grabar

Saturday, October 20

Morning Session—9:30 A.M.

Skin Tests (Cutaneous Intradermal Epidermal and Prausnitz-Küstner Reactions). Technique and Interpretation.....Dr. Holtzer and Professor Wolfromm

Monday, October 22

Morning Session—9:30 A.M.

Nervous Allergic Manifestations.....Professor L'Hermitte
Allergic Migraine.....Professor Valery-Radot
Ocular allergic manifestations.....Dr. Guillaumat

Afternoon Session—2:30 P.M.

Study of Passive Transmission to Animals: Allergic and Bacterial Antibodies. The Schultz-Dale Phenomenon.....Dr. B. N. Halpern

Tuesday, October 23

Morning Session—9:30 A.M.

Allergies Due to Serums and Medications.....Professor Valery-Radot
Allergies Due to Physical Agents.....Professor Valery-Radot

Afternoon Session—2:30 P.M.

Study of Bronchial Movements *in Vivo* and *in Vitro*. Action of Various Broncholytic Agents.....Dr. B. N. Halpern

Wednesday, October 24

Morning Session—9:30 A.M.

Generalizations on the Treatment of Allergic States.....Professor Valery-Radot
Specific Methods of Desensitization.....Professor Wolfromm
Treatment by the Use of Antihistamines.....Professor Valery-Radot

Afternoon Session—2:30 P.M.

Histamine-liberating Substances.....Dr. B. N. Halpern
The Aerosols in Asthma Therapy.....Dr. Blaumoutier
Endobronchial Cinematography in Asthma.....Dr. Dubois de Montreynaud

Thursday, October 25

Morning Session—9:30 A.M.

Treatment with ACTH, Cortisone, Hydrocortisone, and Prednisone.....
Professor Valery-Radot
Various Methods of Treatment.....Professor Valery-Radot

Afternoon Session—2:30 P.M.

Motion Picture on Anaphylaxis and Allergy.

APPROVAL OF RESIDENCIES IN PEDIATRIC ALLERGY

The American Board of Pediatrics, through its subspecialties board of allergy, and the Council on Medical Education and Hospitals of the American Medical Association are developing a program for the approval of residencies in allergy in preparation for certification in that subspecialty. Applications for approval should be submitted to Dr. John McK. Mitchell, Executive Secretary, American Board of Pediatrics, 6 Cushman Road, Rosemont, Pennsylvania.

SECTION ON OPHTHO-OTOLARYNGOLOGY

The Ophtho-Otolaryngology Section of The American College of Allergists has elected the following officers to serve for 1956-1957:

Chairman: Hugh A. Kuhn, M.D., 112 Rimbach Street, Hammond, Indiana
Vice Chairman: Edley H. Jones, M.D., 1301 Washington Street, Vicksburg, Miss.
Secretary: Clyde F. Elkins, M.D., 1626 15th Street, Lubbock, Texas

CALIFORNIA SOCIETY OF ALLERGY

At its regular annual meeting in conjunction with the California Medical Association Convention, on May 1, 1956, at Los Angeles, the California Society of Allergy elected the following officers for 1956-1957:

President—Ben C. Eisenberg, M.D., Huntington Park.
President-elect: Williard S. Small, M.D., Pasadena.
Secretary-Treasurer: William J. Kerr, Jr., M.D., San Rafael.

NORTHERN CALIFORNIA SOCIETY OF ALLERGY

Officers of the Northern California Society of Allergy for the current year are:

President.....M. Coleman Harris, San Francisco
Vice President.....Gardner Stout, M.D., San Mateo
Secretary-Treasurer.....Albert Rowe, Jr., M.D., Oakland

NEW JERSEY ALLERGY SOCIETY

At the annual Atlantic City meeting of the New Jersey Allergy Society, the following officers were elected for the year 1956-57:

President, E. J. Luippold, M.D., Boonton
Vice President, Harry Hershey, M.D., Jersey City
Secretary, Frank H. Feldman, M.D., Newark
Treasurer, Francis A. Pflum, M.D., Asbury Park
Member, Executive Board, Solomon Aronoff, M.D., Jersey City

MICHIGAN ALLERGY SOCIETY

At the Michigan Allergy Society, which met Wednesday, May 16, 1956, a program was presented which included Dr. Jack E. Goodwin, who spoke on "Use of Prantal In Bronchial Asthma," and Dr. James A. McLean, who discussed "Hypothyroidism Following Iodide Treatment of Asthma." Other speakers were Dr. Giles G. Bole, Jr., on "C-Reactive Protein, A Non-Specific Reactant," Dr. Nancy E. Furstenberg, on "Drug Reactions During Anti-Tuberculosis Therapy," and Dr. Edward A. Carr, Jr., on "Relation Between Dose and Response in Allergic Reactions."

At the dinner, Dr. Carl V. Weller's subject was "Leeuwenhoek and the Spirit of Research."

THIRD CONGRESS, INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

The Third International Congress on Allergy of the International Association of Allergology will meet in Paris, October 26 to November 1, 1958. Symposia and sectional meetings will include all phases of allergic diseases and immunology. Inquiries regarding this meeting should be addressed to the secretary, Dr. José Quintero Fossas, Paseo 313, Vedado, Havana, Cuba.

AMERICAN COLLEGE OF PHYSICIANS ELECTS HONORARY FELLOW

Mr. Edward R. Loveland, Philadelphia, Pennsylvania, for more than thirty years Executive Secretary of The American College of Physicians, has been made an Honorary Fellow of the College, the only layman ever so honored. He was presented an illuminated certificate, reading in part:

"As Executive Secretary of the College from 1926-1956 his ability and devotion have been outstanding. His services have been distinguished by his constant adherence to the highest traditions of the medical profession. During these years he has played an essential role in the advancement of the program of the College in the fields of Medical Education and Medical Science."

ACADEMY OF PSYCHOSOMATIC MEDICINE

The Third Annual Meeting of the Academy of Psychosomatic Medicine will be held at the Hotel Plaza, New York City, Thursday through Saturday, October 4-6, 1956. Mornings will be devoted to papers on various phases of psychosomatic medicine as related to heart disease, internal medicine, duodenal ulcer, and psychotherapy as directed toward the physician in general practice. There will be panel discussions in the afternoon, followed by general discussion of the papers presented. On Thursday, the panel will be on "Obesity, a Psychosomatic Dilemma," and six members will each speak for ten minutes on a different phase of obesity. On Friday, the discussion will center around "Vertigo, Headaches and Insomnia," and the Saturday afternoon panel will discuss "Psychosomatic Aspects of Allergic Disease." Further information about this meeting may be obtained from the secretary, Dr. Ethan Allan Brown, 75 Bay State Road, Boston, Massachusetts.

NEWS ITEMS

WORLD MEDICAL ASSOCIATION

The tenth general assembly of the World Medical Association will be held in Havana, Cuba, October 9-15, 1956. The program is not yet completely available, but it will be an interesting one. Plenary sessions, social events, including the annual dinner, and an all-day excursion to the famous Veradero Beach will make the meeting a memorable occasion.

The Cuban Medical Association has made reservations in the leading hotels available through the Secretariat. Accommodations should be requested early. Early pre-registration also assures early reservations for the social functions and excursions.

Inquiries should be sent to Dr. Louis H. Bauer, Secretary-Treasurer, The World Medical Association, 10 Columbus Circle, New York 19, N. Y.

NINTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

The Ninth International Congress on Rheumatic Diseases will be held at Toronto, Ontario, Canada, from June 23 to 28, 1957. This quadrennial function of La Ligue Internationale contre le Rhumatisme will be held under the auspices of the Canadian Rheumatism Association. The Program Committee invites contributions to the scientific program of the Congress and is anxious to receive reports on current clinical or basic research dealing with any aspect of the rheumatic diseases. Those offering papers for consideration should submit a 200-300 word abstract not later than January 1, 1957. Abstracts should be submitted in triplicate in the language in which the paper is to be read. If an abstract is submitted in a language other than English, it will be helpful, though not essential, if it can be accompanied by an English translation. All correspondence should be directed to: The Ninth International Congress on Rheumatic Diseases, Post Office Box 237, Terminal "A", Toronto, Ontario, Canada.

ALLERGY SESSION, AMERICAN MEDICAL ASSOCIATION

The Allergy Session at the annual meeting of the American Medical Association in Chicago in early June was very well attended, and the physical arrangements for the meeting—loud speaker system, acoustics, and lighting arrangements—were excellent. Dr. Stanley Hampton conducted the meeting until the intermission, when the program was taken over by Dr. Lawrence J. Halpin, who also conducted the question and answer period. There was an attendance of almost a thousand at the nine lectures. The program was as follows: "Allergy and the Generalist," by Mayer A. Green, M.D., Pittsburgh, Pennsylvania; "The Management of Allergy —As It Is—As It Might Be," by Samuel M. Feinberg, M.D., Chicago, Illinois; "The Role of Tranquilizing Drugs in Allergy," by Ben C. Eisenberg, M.D., Huntington Park, California; "The Allergenicity of Tranquilizing Drugs," by Clarence Bernstein, M.D., Orlando, Florida; "The Use of Prednisone and Prednisolone in the Treatment of Allergic Diseases," by Earl B. Brown, M.D., New York City; "The Topical Use of Hydrocortisone Hemisuccinate (Solu Cortef), Fluorohydrocortisone (F-Cortef), and Prednisolone (Delta Cortef) on the Allergic Mucous Membrane: A Controlled Study," by William C. Grater, M.D., Dallas, Texas; and "The Response of Childhood Asthma to IPPB Aerosol Therapy," by Roy F. Goddard, M.D., Albuquerque, New Mexico.

THIRD EUROPEAN CONGRESS OF ALLERGOLOGY

The Third European Congress of Allergology, organized by the Italian Society of Allergology and sponsored by the International Association of Allergolgy, will be held in Florence, Italy, September 12-15, 1956.

The Organizing Committee of the Congress is: Honorary President, Prof. C.

Frugoni; President, Prof. A. Lunedei; Members: Prof. G. B. Belloni, Prof. V. Chini, Prof. P. Di Mattei, Prof. G. Favilli, Prof. F. Flarer, Prof. M. Lusena, Prof. M. Magrassi, Prof. G. Melli, Prof. P. Sangiorgi; General Secretary: Prof. U. Serafini.

Reports, subjects to be presented and tentative list of speakers are as follows:

1. GENESIS AND LOCALIZATIONS OF ANTIBODIES
   Speakers: Oakley (Great Britain), Pasteur Vallery Radot and colleagues (France), Van Dishoeck (Holland), Colldahl (Sweden), Melli (Italy), Schmidt (Germany), Kleinsorge (Germany), Halpern (France).
2. ALLERGY AND THE NEURO-VEGETATIVE SYSTEM
   Speakers: Lunedei (Italy), Werner (Germany), Farrerone (Spain), MacDowall (Great Britain), Bovet and Sicuteri (Italy), Halpern (France), Panzani and Gastaut (France), Charpy (France), Hahn (Germany), Zacco (Italy).
3. INCREASE IN PRESENT-DAY ALLERGY
   Speakers: Di Mattei (Italy), Hansen (Germany), Belloni (Italy), Surinyach (Spain), Spoujitch and Colleagues (Jugoslavia), Sangiorgi (Italy), Van der Werff (Holland), Jadassohn (Switzerland), Sidi (France), Flarer (Italy), Rajka (Hungary), Lucherni and Cervini (Italy).
4. MECHANISM OF DELAYED REACTIONS
   Speakers: Bruun (Denmark), Pepys (Great Britain), Charpy (France).
5. CLASSIFICATION AND TERMINOLOGY IN ALLERGY
   Speakers: Pearson (Great Britain), Wagener (Germany).
6. STANDARDIZATION OF ALLERGEN EXTRACTS
   Speaker: Augustin (Great Britain).

For further information, please address the General Secretary of the Congress: Istituto Di Patologia Medica, Viale Morgagni, Florence, Italy.

FOURTH INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

The Fourth International Congress of Internal Medicine, organized by the International Society of Internal Medicine, will be held in Madrid, Spain, September 19-23, 1956. Two themes will provide the basis for the discussions at this congress —The role of the adrenals in the pathogenesis and evolution of internal diseases, and bronchial asthma and emphysema. In addition there will be a symposium on "The Present Situation of Internal Medicine." Official languages of the congress will be English, French, German and Spanish. Scientific and industrial exhibits will be held in conjunction with the congress. Further information about this meeting may be obtained from the Secretariat of the Congress, Hortaleza No. 90, Madrid, Spain. Prof. N. Svartz of Stockholm, Sweden, is president of the International Society of Internal Medicine, and Prof. C. Jiménez Diaz of Madrid is president of the congress committee.

WOMEN'S AUXILIARY ANNOUNCES TWO AWARDS

The Women's Auxiliary of The American College of Allergists announces that for the Thirteenth Annual Meeting of the College two prizes will be offered.

The BELA SCHICK AWARD, a prize of $150 and a Certificate of Award, will be made for the best paper written by an Associate Fellow of The American College of Allergists for presentation at the annual convention of the College.

The CLEMENS VON PIRQUET AWARD will be made for the best paper written by an intern or resident on any aspect of allergy. This paper will also be presented at the annual convention of the College, and a Certificate of Award will be made and a prize of $75 given to defray traveling expenses to the convention.

All papers are to be judged by a committee consisting of the Program Commit-

tee of the Thirteenth Annual Meeting and of members of the Editorial Board of the ANNALS OF ALLERGY. Awards and checks will be presented at the annual meeting in Chicago next March.

ETHAN ALLAN BROWN WINS ESSAY CONTEST

The editor of THE ANNALS OF ALLERGY entered an essay entitled, "The General Practitioner and Drug Allergy," in the annual Mississippi Valley Medical Society Essay Contest for 1956. It was awarded second place. The certificate of merit will be presented at the banquet given by the Society at the Hotel Morris in Chicago, Thursday evening, September 27, 1956. The winning essay and the essay which was awarded third place will appear in the January, 1957, issue of the *Mississippi Valley Medical Journal.*

NEWS OF MEMBERS

John P. McGovern, M.D., Houston, Texas, has resigned his position as Associate Professor of Pediatrics and Allergy at Tulane University School of Medicine, New Orleans, Louisiana, to take over the allergy practice of the late Ralph Bowen, at 3509 Montrose Boulevard, Houston. Dr. McGovern is certified by the American Board of Pediatrics and the Subspecialty Board in Pediatric Allergy, but will confine his practice entirely to allergy. He will continue his teaching activities, however, at the Baylor University School of Medicine and the University of Texas Postgraduate School of Medicine.

WOMEN'S AUXILIARY—SECOND ANNUAL MEETING

The 146 women who registered for the second annual meeting of the Auxiliary at the Hotel New Yorker, New York City, in April, enjoyed a wonderful week.

A fine Hostess Committee, chaired by Mrs. M. Murray Peshkin, New York, was constantly in attendance at the Hospitality Room to welcome members and guests. They obtained difficult-to-get theatre and TV tickets and offered many other courtesies. They assisted at the coffee breaks given on April 15, 16 and 17, which were made possible through the courtesy of Charles Pfizer & Company, Brooklyn.

At the business meeting, the membership voted into office the following:

President—Mrs. Ethan Allan Brown, Massachusetts
President-Elect—Mrs. J. Warrick Thomas, Virginia
Vice President—Mrs. Harry L. Rogers, New Jersey
Secretary—Mrs. R. Dale Dickson, Kansas
Treasurer—Mrs. Ralph A. Scala, Illinois
Historian—Mrs. Maurice Barnes, Texas
Directors:—Mrs. Morris A. Kaplan, Illinois; Mrs. Philip M. Gottlieb, Pennsylvania; Mrs. Louvane A. Fox, New Hampshire.

It was voted to carry out a program in Education, the committee of which will act with the approval of The American College of Allergists, and to change the fiscal year to begin April 1 and to end on March 31.

After the business meeting, a luncheon was served in the White and Gold Room of the Hotel Plaza. Each member was presented with a powder compact through the courtesy of Marcelle Cosmetics, Chicago, Illinois.

The guest of honor, Dr. Horace S. Baldwin, President of the American Foundation of Allergic Diseases, gave an interesting and informative talk on the Foundation. Dr. Baldwin was presented a check of $500 as an expression of the interest of the Auxiliary in the aims of the Foundation.

On Friday morning, the Auxiliary attended breakfast at the Charleston Garden of B. Altman & Company. This was followed by a fashion show.

Members of the Auxiliary were saddened to learn of the untimely deaths of Dr. Ralph Bowen of Texas, and Dr. John Peters of Illinois. Deepest sympathy is extended to their wives and their families.

MRS. ETHAN ALLAN BROWN, *President*
MRS. R. DALE DICKSON, *Secretary*

BOOK REVIEWS

THE DOCTOR IN PERSONAL INJURY CASES. Harold A. Liebenson, Member of Illinois, Chicago and American Bar Associations. 123 pages, including index. Chicago: The Year Book Publishers, Inc. 1956. $4.00.

In his foreword, Dr. Sidney S. Greenspahn, a medicolegal consultant of thirty years' experience, states that "This book is a worthwhile addition to the physician's and lawyer's library." The author, Harold A. Liebenson has written exactly the type of book which should be required reading for both physicians and attorneys.

After devoting a chapter to the definitions of the usual legal terms, he discusses "The Doctor's Importance In a Personal Injury Case." He then gives the details of a "medical report." From this he leads into court procedure, appearance in court and then that most difficult aspect of medicolegal work, "Opinion Evidence and Hypothetical Questions."

He describes the details of the direct examination and of the cross examination.

The last chapter of the book describes the nature of malpractice, privileged communication and workmen's compensation.

A great many physicians are fearful of court appearances because they are not always familiar with the procedures involved. A careful reading and re-reading of this book will do a great deal to bolster their self confidence.—E.A.B.

1956 MEDICAL PROGRESS: A REVIEW OF MEDICAL ADVANCES DURING 1955. Edited by Morris Fishbein, M.D. Cloth, 389 pages, including index. New York: Blakiston Division, McGraw-Hill Book Co., Inc., 1956. Price $5.50.

Any attempt to summarize in a single volume the multitudinous medical and surgical advances of a whole year obviously represents an ambitious project. This survey, the fourth in a series, reviewing the progress of the year 1955, succeeds surprisingly well.

As the editor, Morris Fishbein, points out, the current epoch is marked by an increased understanding of the mechanisms and control of the nervous system, the spasmodic and convulsive disorders being for the first time approached from the standpoint of their biochemical origins. Each of the twenty-one chapters is written by a recognized authority and covers a single subject. While the discussions are bolstered by a large number of references, they comprise much more than a series of disconnected abstracts, since the material is grouped under appropriate headings and subsections, and each author has added the imprint of his own viewpoints.

Of special interest to readers of the ANNALS is the chapter on "Allergy" by G. T. Brown, with sections on penicillin reactions, pollen counting, corticosteroids, antihistamines (containing a useful list of the trade and generic names), Alevaire® Aerosol. Several useful and practical therapeutic methods are incorporated. Of more than passing interest are the chapters on "Laboratory Procedures," including a discussion of C-reactive protein determinations, by R. B. H. Gradwohl, and on "Poliomyelitis Vaccine" by P. H. Long. The collagen diseases are reviewed by E. W. Boland in a chapter on "Rheumatic Diseases." Other representative chapters —it is not possible to mention them all—include "Diabetes" by E. P. Joslin, "Gastroenterology" by F. B. Brooks and D. J. Sandweiss, "Neurology" by F. M. Forster, "Dermatology" by H. Rattner, "Ear, Nose, and Throat" by F. L. Lederer and B. J. Soboroff, and "New Drugs" by P. L. Wermer.

Naturally, there are limitations in such a bird's eye view. Many of the sections are of necessity brief. Likewise, some overlapping of topics is inevitable in the various chapters. Discussion of corticoid and corticotropic therapy, the ataraxic agents, the Salk poliomyelitis vaccine, and cardiac surgery recurs repeatedly. This

is not without its advantages, since it permits comparison of the differing opinions of the various contributors. A mild degree of surprise may be expressed at the absence of any reference to the subjcts of agammaglobulinemia and of pyruvic acid metabolism, both of which have been extensively investigated in the past year. Despite these minor criticisms, this is a most valuable survey volume, parts of which may be read and the remainder skimmed, to the advantage of every physician.

TOLERANCE ET INTOLERANCE AUX PRODUITS COSMETIQUES; CLINIQUE, LABORATOIRIE. Edwin Sidi, M.D., with the collaboration of J. Bourgeois-Spinasse. Paris: Masson et Cie, 1955.

This volume presents a fine summary of the problems connected with irritations due to cosmetic products. In the introductory chapters the authors discuss some of the physiologic factors which influence tolerance to cosmetics, such as the fatty materials on the skin, the pH and the pigment. A clear differentiation is made between reactions due to primary irritants and sensitizers. There is a detailed discussion of the patch test technique with illustrations of the appearance of allergic eczematous responses and primary irritant responses in patch tests.

Ingredients are listed of the various cosmetic products which can cause eruptions and the chemical basis which underlies their action and produces some of their ill effects.

There are excellent illustrations of eruptions caused by cosmetic products as well as of the patch test reactions elicited in the particular cases. Short chapters deal with pigmentary disturbances due to cosmetics, occupational dermatoses due to cosmetics and legal aspects of dermatoses caused by cosmetics.

This book was written by authors who have had a very wide experience in the field of dermatologic allergy and of dermatologic aspects of cosmetology. It can be highly recommended to all those who are interested in the cutaneous effects of cosmetics.—*R.L.B.*

ENZYMATIC CONCEPT OF ANAPHYLAXIS AND ALLERGY. Z. Z. Godlowski, M.D. (Cracow), Ph.D. (Edin.), M.R.C.P. (Edin.), Research Fellow of the Carnegie Trust, Edinburgh. Foreword by A. Murray Drennan, M.D., F.R.C.P.E., F.R.S.E., Professor of Pathology, University of Edinburgh. 120 pages, including index, illus. Edinburgh and London: E. & S. Livingstone, Ltd., 1953. Price $3.50.

In his foreword, Dr. Drennan, professor of pathology at the University of Edinburgh, states that, "This is hardly a book for the beginner, but for the scientific clinician, the physiologist, and the pathologist it should be interesting, informative, and stimulating." The book itself has caused so much comment that it is herewith belatedly reviewed.

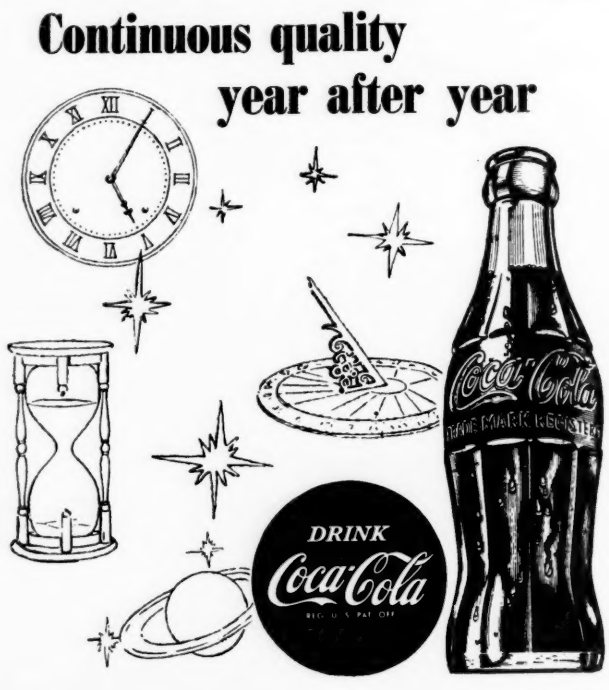
Dr. Godlowski is a Research Fellow of the Carnegie Trust at the University of Edinburgh. For his Ph.D. degree he re-examined the ever-fascinating problem of the eosinophil cell. This lead to the study of the groups of disorders which were due to anaphylaxis and then to those which were superficially similar but nonanaphylactic in origin. His studies soon became involved in the manifestations of stress and the effects of the corticosteroids and pituitary hormones not only in the hormonal dyscrasias, but with the disturbances in enzymatic proteolysis.

The author admits that the theories involved are not new. He stresses the fact that they were advanced by others as early as 1909, but rejected because of a lack of conclusive evidence and apparently incompatible experimental findings. But, with recent developments in histochemistry and with modern knowledge of submicroscopic cellular structure, there is enough new evidence for support of the enzyme theory to warrant re-examination of its tenets. This Dr. Godlowski does with rare skill, although he admittedly omits the information available in the associated disciplines of biochemistry and physicochemistry.

Dr. Godlowski's basic theory is easily abstracted. There is the antigen-antibody reaction as a cause of anaphylaxis. The reaction may occur with no signs of anaphylaxis. There may be, as well, anaphylaxis with no previous antigen-antibody reaction. When anaphylaxis is truly seen, it results from the "failure of the antigen-antibody reaction." He suggests that the reaction between antigen and antibody and also the process of sensitization may be two different patterns of response, although the "failure" or imperfection of the former may cause the latter.

An antigen is not necessarily toxic. As we know, its injection into nonsensitized tissues causes no anaphylaxis. If the dose is a sensitizing one, toxic proteoses are produced intracellularly. A second shocking dose initiates "toxic proteolysis" which liberates toxic degradation products responsible for the anaphylactic effects.

Recent work with isotopes shows that antigens do not only enter into every body cell, but become part of the cytoplasm of every cell, and of each cell component including the nucleus, the microsomes and mitochondria. When so incorporated into the basic structure of the cell they can be transmitted to the next generation. When antibody formation results there are five major types which may be lysins, precipitins, agglutinins, opsonins and complement fixers. Proteolytic antibodies may react with the protein of the antigen to result in either "nontoxic" or in "toxic" catabolites. The latter is what we see in reacting patients. Every reader will not be convinced, but the hypothesis, if true, is thought provoking.

The remaining chapters are clear and not so controversial.

Anaphylaxis is physiologic when tissue "counter-measures" balance the ill-effects of the presence of unsplit protein. It is pathologic when such balance is not achieved.—*E.A.B.*